

PAPER NAME

**13472989_YiminCui_Targetingintegrinpa
thwaysmechanismsandadvancesinthera
py.docx**

WORD COUNT

20014 Words

CHARACTER COUNT

120971 Characters

PAGE COUNT

36 Pages

FILE SIZE

932.0KB

SUBMISSION DATE

Nov 13, 2022 9:08 PM GMT+8

REPORT DATE

Nov 13, 2022 9:10 PM GMT+8

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1 **Review Article**

2 **Targeting integrin pathways: mechanisms and advances in**
3 **therapy**

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ABSTRACT

Integrins are considered the main cell adhesion transmembrane receptors that play multifaceted roles as extracellular matrix (ECM)-cytoskeletal linkers and transducers in biochemical and mechanical signals between cells and their environment in a wide range of states in health and diseases. Integrin functions are dependable on a delicate balance between active and inactive status via multiple mechanisms, including protein-protein interactions, conformational changes, and trafficking. Due to their exposure on the cell surface and sensitivity to molecular blockade, integrins have been investigated as pharmacological targets for nearly 40 years, but given the complexity of integrins and sometimes opposite characteristics, targeting integrin therapeutics has been a challenge. To date, only seven drugs targeting integrins have been successfully marketed, including abciximab, eptifibatide, tirofiban, natalizumab, vedolizumab, lifitegrast and carotegast. Currently, there are approximately 90 kinds of integrin-based therapeutic drugs or imaging agents in clinical studies, including small molecules, antibodies, synthetic mimic peptides, antibody-drug conjugates (ADCs), chimeric antigen receptor (CAR) T-cell therapy, imaging agents, etc. A serious lesson from past integrin drug discovery and research efforts is that successes rely on both a deep understanding of integrin regulatory mechanisms and unmet clinical needs. Herein, we provide a systematic and complete review of all integrin family members and integrin-mediated downstream signal transduction to highlight ongoing efforts to develop new therapies/diagnoses from bench to clinic. In addition, we further discuss the trend of drug development, how to improve the success rate of clinical trials targeting integrin therapies, and the key points for clinical research, basic research and translational research.

INTRODUCTION

Integrins have emerged as cell adhesion transmembrane receptors that serve as extracellular matrix (ECM)-cytoskeletal linkers and transduce biochemical and mechanical signals between cells and their environment in a wide range of states in health and diseases since their discovery in the 1980s¹⁻³ (Fig. 1). In mammals, each integrin heterodimer comprises an α -subunit and a β -subunit in a noncovalent complex, and 18 α - and 8 β -subunits create 24 functionally distinct heterodimeric transmembrane receptors⁴. Each α or β subunit contains a large ectodomain, a single-span helical transmembrane domain, and a short cytosolic tail, with the exception of $\beta 4$ ⁵. The majority of integrin heterodimers contain the $\beta 1$ subunit and αv subunit. The $\beta 1$ subunit can form heterodimeric complexes with 12 α -subunits, but $\beta 4$, $\beta 5$, $\beta 6$, and $\beta 8$ only interact with one α -subunit. Most α -subunits only form one kind of complex with one β partner, while $\alpha 4$ and αv interact with more than one β partner, including $\alpha 4 \beta 1$, $\alpha 4 \beta 7$ and $\alpha v \beta 1$, $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha v \beta 6$, $\alpha v \beta 8$.

The “integrin” terminology originates from its function as the integral membrane protein complex bridging the ECM to the cytoskeleton⁶. The first integrins discovered were isolated based on their binding ability to fibronectin¹. Typically, integrins can interact with a plethora of ECM proteins, and most of them contain small peptide sequences as integrin recognition motifs^{7,8}. The targeting integrin sequences can be as simple as the Arg-Gly-Asp (RGD) or Leu-Asp-Val (LDV) tripeptides or more complex as GFOGER peptide⁹⁻¹¹. According to the different binding characteristics of integrins, integrins can be divided into four types: leukocyte cell adhesion integrins, RGD-binding integrins, collagen (GFOGER)-binding integrins, and laminin-binding integrins¹². Classically, there are 8 members in the RGD-binding family of integrins: $\alpha v \beta 1$, $\alpha v \beta 3$, $\alpha v \beta 5$, $\alpha v \beta 6$, $\alpha v \beta 8$, $\alpha 8 \beta 1$, $\alpha 5 \beta 1$, and $\alpha IIb \beta 3$. The RGD peptide is the common binding motif of these RGD-binding integrins in the ECM (e.g., fibronectin, osteopontin, vitronectin, and fibrinogen)¹³.

Leukocyte cell adhesion integrins consist of 8 members, including $\alpha 4\beta 1$, $\alpha 9\beta 1$, $\alpha L\beta 2$, $\alpha M\beta 2$, $\alpha X\beta 2$, $\alpha D\beta 2$, $\alpha 4\beta 7$, and $\alpha E\beta 7$. Integrins $\alpha 4\beta 1$, $\alpha 4\beta 7$, $\alpha 9\beta 1$ and $\alpha E\beta 7$ also recognize short specific LDV peptide sequences, and an LDV motif is also present in fibronectin. $\beta 2$ is the most common integrin that mediates leukocyte adhesion and migration, which is characterized by sites within ligands that are structurally similar to the LDV motif¹⁴. The four collagen-binding integrins ($\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha 11\beta 1$) recognize the triple helical GFOGER sequence in the major collagens, but their binding ability *in vivo* depends on the fibrillar status and the accessibility of interactive domains¹². Four non- α I domain-containing laminin-binding integrins ($\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 7\beta 1$, and $\alpha 6\beta 4$) can bind with laminins. In addition, three α I domain-containing integrins ($\alpha 10\beta 1$, $\alpha 2\beta 1$, and $\alpha 1\beta 1$) can form a distinct laminin/collagen-binding subfamily. The expression of these integrin isoforms is tissue specific and developmentally regulated; however, a full understanding of their role is still lacking. Beyond classical ECM mediators, integrins are also reported to interact with a diversity of non-ECM proteins on the surfaces of prokaryotic, eukaryotic, and fungal cells, as well as a range of viruses^{15,16}. In addition, integrins can also be exploited as cell surface receptors for growth factors, hormones and polyphenols¹⁷.

The wide range of ECM and non-ECM molecules makes integrins integral mediators of cell biology in mass. Integrin functions are dependable on a delicate balance between active and inactive status via multiple mechanisms, including protein–protein interactions, conformational changes, and trafficking⁴. These processes are triggered through “inside-out” signals and “outside-in” signals, resulting either from interacting with proteins such as α -actinin, talin, vinculin, and paxillin to the cytoplasmic β -integrin tail or from binding to ECM ligands and recruiting adhesion complexes^{18,19}. Upon adhesion, cytoskeletal proteins are linked to the integrin β -subunit cytoplasmic tail²⁰. Most integrin adhesion complexes (IACs) include focal adhesions (FAs), fibrillar adhesions, immunological synapses, and podosomes²¹. The primary intracellular downstream signaling mediators of integrins refer to focal adhesion kinase (FAK), Src-family protein tyrosine kinases, and integrin-linked kinase (ILK)²². Integrins transduce mechanical and biochemical signals to promote cell proliferation, adhesion, spreading, survival and ECM assembly and remodelling.

Due to their exposure on the cell surface and sensitivity to molecular blockade, integrins have been investigated as pharmacological targets for nearly 40 years, and a certain amount of current efforts involving integrin therapeutics continues to surprise (Fig. 1). In 2022, the Lasker Prize in Medicine was awarded to Richard Hynes, Erkki Ruoslahti, and Timothy Springer for groundbreaking research in the discovery of integrins, which aroused great concern about the field of integrins. The integrin discovery history started in the 1980s. The first identification of integrin family member is $\alpha IIb\beta 3$, and the first integrin-targeting drug was Abciximab, approved in 1994 as an $\alpha IIb\beta 3$ antagonist²³. Intravenous $\alpha IIb\beta 3$ inhibition has been a major success in the treatment of coronary artery disease, but current oral $\alpha IIb\beta 3$ antagonists have failed to achieve end points but potentially induce a direct toxic effect with prothrombotic mechanisms²⁴. In 2003, a nanotherapeutic agent, a nanoparticle coupled to an $\alpha v\beta 3$ -targeting ligand for delivering genes, was first reported to selectively target angiogenic blood vessels in tumor-bearing mice²⁵. In 2003, the αL antagonist Efalizumab was approved but withdrawn in 2009 due to the adverse effect of progressive multifocal leukoencephalopathy. In 2004, the pan- $\alpha 4$ antagonist natalizumab was approved for multiple sclerosis. Then, there is a real gap in the market for targeting integrins. The failure of cilengitide in clinical trials on glioblastoma treatment had a huge impact on targeting αv -integrin drug discovery²⁶. To date, there are no approved drugs targeting αv -integrin. In 2014 and

2016, vedolizumab and lifitegrast, targeting $\alpha 4\beta 7$ and $\alpha L\beta 2$ for the treatment of inflammatory bowel disease and dry eye disease, respectively, were approved. In 2017, CAR T cells targeting integrin were investigated²⁷. In 2022, there will be a large breakthrough targeting integrin, including the phase III clinical trial success of the ^{99m}Tc -3PRGD2 imaging agent, the approval of Carotegrast, as the first oral anti-integrin drug, by Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and the phase IIa positive results of the oral $\alpha v\beta 6/\alpha v\beta 1$ antagonist PLN-74809. To date, the U.S. Food and Drug Administration (FDA) has approved a total of 7 drugs targeting integrins²⁸. Currently, there are approximately 90 kinds of integrin-targeting therapies in clinical trials, including integrin antagonists and imaging agents, including small molecules, antibodies, synthetic mimic peptides, antibody-drug conjugates (ADCs), CAR T-cell therapy, imaging agents, etc. A serious lesson from past integrin drug discovery and research efforts is that successes rely on both a deep understanding of integrin regulatory mechanisms and unmet clinical needs.

Several recent reviews have analyzed the details of both biochemical and mechanical integrin regulation, integrin structure, integrin roles in cancer and fibrosis disease, RGD-binding integrin drug discovery, especially small-molecule inhibitors of the αv integrins, the mechanism of endocytosis, exocytosis, intracellular trafficking, and mechanotransduction^{3,4,28,29}. Herein, we attempt to provide a systematic and complete review of all integrin family members and integrin-mediated downstream signal transduction to highlight ongoing efforts to develop new therapies/diagnoses. Furthermore, we also provide insight into the trend of drug development, how to improve the success rate of clinical trials of integrin-targeting therapies, and the key points for clinical research, basic research and translational research.

STRUCTURE AND FUNCTION OF THE INTEGRIN FAMILY

Since the crystal structure of $\alpha v\beta 3$ was available in 2001, conformational changes in integrin ectodomains have been illustrated. The ectodomain of an α -subunit contains four extracellular domains: a seven-bladed β -propeller, a thigh, and two calf domains (Fig. 2 a, b). The common structure of different α -subunits present in their extracellular domain are seven repeat motifs, which fold into a seven-bladed propeller structure on the upper surface, and on the lower surface of blades 4–7, divalent cation-binding sites are located (Fig. 2 a, b). Half of the integrin α subunits (i.e., $\alpha 1$, $\alpha 2$, $\alpha 10$, $\alpha 11$, αD , αX , αM , αL) contain a domain of 200 amino acids, known as the inserted (I) domain or αI domain, which is located between blades 2 and 3 of the β propeller. Integrins with an αI domain bind to ligands through this domain³⁰. The structure of an αI domain contains a metal ion-dependent adhesion site motif (MIDAS), which is the major ligand-binding site³¹.

The crystal structure of the αI domain suggests three distinct conformations, termed bent closed, extended closed and extended open conformations³² (Fig. 2 c). They differ not only in the coordination of the metal in the MIDAS but also in the arrangement of the $\beta F-\alpha 7$ (F/ $\alpha 7$) and the disposition of the $\alpha 1$ and $\alpha 7$ helices^{32,35}. In the active state of the αI domain, a C-terminal glutamate from the αI domain ligates the βI MIDAS and further stabilizes the high-affinity conformations³⁴. The ectodomain of the β subunit comprises seven domains with complex domain insertions (Fig. 2 a, b): a βI domain with insertion in the hybrid domain, plexin-semaphorin-integrin (PSI), four cysteine-rich epidermal growth factor (EGF) modules, and a beta tail domain (βTD) domain³⁵. The integrin β subunit I domain is homologous to the αI domain. Resting integrins exist in a bent-closed conformation, which is unable to bind ligand, and Integrins can extend and form a high-affinity conformation with an open headpiece^{36,37}. The open headpiece conformation is induced with binding ligands, and this activated state possesses high binding affinity. Ligand binding further

provides the energy for conformational change triggering outside-in signaling. In addition, for induction of the high-affinity state, the open headpiece conformation could be produced artificially by mutations³⁸. For example, it was reported that mutations in β TD residues in CD11b/CD18 integrins could lead to constitutive activation and outside-in signaling responses³⁵.

All α I domain less integrins bind to the ligand directly using a binding pocket that is formed by the β -propeller/ β I domain interface²¹. In this ligand binding pocket, three divalent metal ion binding sites are concentrated on the ligand binding sites of the β I domain in a linear arrangement³⁹. The middle site, like the α I domain, called MIDAS, whose metal ion directly coordinates the side chain of the acidic residue characteristic of the integrin ligands, and the two outer sites, adjacent metal ion-dependent binding site (ADMIDAS) and ligand-associated metal binding site (LIMBS) or synergistic metal ion-binding site (SyMBS)^{40,41}, can also bind Mn^{2+} , Mg^{2+} and Ca^{2+} , sharing some coordinating residues in common with MIDAS⁴²⁻⁴⁴. The divalent metal cation on MIDAS is essential for the binding of integrin ligands. Some studies have shown that after the metal ions in MIDAS are removed by residue mutations, the ligand fails to bind to integrins, which suggests that MIDAS is critical for coordination and binding⁴³.

The first crystal structure of $\alpha v\beta 3$ bound to a mutant of fibronectin revealed the structure basis underlying pure antagonism, a central π - π interaction between Trp1496 in the RGD-containing loop of the high affinity form of the 10th type III RGD-domain of fibronectin (FN) (hFN10) and Tyr122 of the $\beta 3$ -subunit that blocked conformational changes triggered by a wild-type form (wtFN10) and trapped hFN10-bound $\alpha v\beta 3$ in an inactive conformation⁴⁵. Then, the cyclic peptide CisoDGRC and small-molecule antagonists of $\alpha IIb\beta 3$ and $\alpha v\beta 3$ were reported to retain high affinity without apparently inducing the conformational change in $\alpha v\beta 3$ by the same mechanism, interacting with $\beta 3$ Tyr122 on the $\beta 1$ - $\alpha 1$ loops and preventing its movement toward MIDAS, which is a key element in triggering conformational change⁴⁶⁻⁴⁸. Recently, Lin et al.⁴⁹ proposed that the water molecule between the Mg^{2+} ion and the MIDAS serine side chain is also important for the integrin conformational change, and expulsion of this water is a requisite for the transition to the open conformation. Therefore, direct evidence for distinct functional roles for conformational change is still acquired for integrin-targeting drug development.

RGD-binding integrins

RGD-binding integrins refer to a class of integrins that bind with the tripeptide motif Arg-Gly-Asp in ECM proteins, including $\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$, $\alpha v\beta 8$, $\alpha 5\beta 1$, $\alpha 8\beta 1$, and $\alpha IIb\beta 3$ ^{50,51} (Fig. 3).

Integrin $\alpha v\beta 1$ primarily binds with transforming growth factor- β (TGF- β), fibronectin, osteopontin, and neural cell adhesion molecule L1⁵². In fibroblasts, such as hepatic stellate cells and pulmonary fibroblasts, integrin $\alpha v\beta 1$ -induced TGF- β activation is important in ECM accumulation^{53,54}. It also mediates the adhesion of osteoblasts to connective tissue growth factor, which induces cytoskeleton reorganization and cell differentiation⁵⁵. Recently, integrin $\alpha v\beta 1$ was identified as a regulator that mediates the vascular response to mechanical stimulation⁵⁶.

Integrin $\alpha v\beta 3$ is one of the earliest integrins to be studied. Because of its specific binding with vitronectin, integrin $\alpha v\beta 3$ was originally called the vitronectin receptor. However, further studies found that integrin $\alpha v\beta 3$ also binds with many other ligands, such as TGF- β , fibronectin, osteopontin, neural cell adhesion molecule L1, fibrinogen, von Willebrand factor, thrombospondin, fibrillin, and tenascin⁵². It is widely expressed in mesenchyme and blood vessels, smooth muscle cells, fibroblasts, and platelets⁵⁷. Integrin $\alpha v\beta 3$ participates in angiogenesis, ECM regulation, vascular

smooth muscle cell migration, and osteoclast adhesion to the bone matrix⁵⁷. In addition, integrin $\alpha\text{v}\beta 3$ expressed in leucocytes participates in regulating monocyte, macrophage, and neutrophil migration and dendritic cell and macrophage phagocytosis, which regulates inflammation progression^{58,59}.

Integrin $\alpha\text{v}\beta 5$ binds with TGF- β , osteopontin, vitronectin, bone sialic protein, thrombospondin, and nephroblastoma overexpressed (NOV, also known as CCN3)⁵². Integrin $\alpha\text{v}\beta 5$ -induced TGF- β activation is involved in various physiological processes, such as wound healing mediated by myofibroblasts⁶⁰, matrix molecule synthesis by airway smooth muscle⁶¹, and type I procollagen expression in skin fibroblasts⁶². The binding of integrin $\alpha\text{v}\beta 5$ with vitronectin is essential for cerebellar granule cell precursor differentiation by regulating axon formation⁶³. In addition, integrin $\alpha\text{v}\beta 5$ is highly expressed in mature intestinal macrophages and mediates macrophage phagocytosis of apoptotic cells^{64,65}.

Integrin $\alpha\text{v}\beta 6$ primarily binds with TGF- β , fibronectin, osteopontin, and a disintegrin and metalloproteinase (ADAM)^{52,66}. It is an important activator of TGF- β , which regulates innate immunity and anti-inflammatory surveillance in the lungs, junctional epithelium of the gingiva, skin, and gastrointestinal tract⁶⁷⁻⁶⁹. In addition, it participates in the process of tooth enamel formation⁶⁸. Studies have reported that $\beta 6$ subunit of $\alpha\text{v}\beta 6$ integrin (ITGB6) knockout significantly increases the risk of emphysema⁷⁰, causes hypomineralized amelogenesis imperfecta⁷¹, promotes skin inflammation and hyperplasia⁶⁸, and accelerates skin wound repair⁷².

Integrin $\alpha\text{v}\beta 8$ is a receptor for TGF- β , which activates TGF- β signal transduction by binding with TGF- β ⁷³. Integrin $\alpha\text{v}\beta 8$ -mediated TGF- β activation is involved in regulating neurovascular development, immune cell recruitment and activation, and stem cell migration or differentiation (such as neuroblast chain and neural stem cell migration, nonmyelinating Schwann cell and mesenchymal stem cell differentiation)⁷⁴.

Integrin $\alpha 5\beta 1$ binds with numerous ligands, such as fibronectin, fibrinogen, fibrillin, osteopontin, and thrombospondin⁷⁵. Owing to its diversity of ligands, integrin $\alpha 5\beta 1$ is involved in numerous physiological processes, including promoting cell migration⁷⁶, invasion⁷⁷, proliferation⁷⁸, and aging⁷⁹. The normal function of T cells is also inseparable from the participation of integrin $\alpha 5\beta 1$, which affects the inflammatory process. In addition, integrin $\alpha 5\beta 1$ is adverse for the formation of bone tissue, and upregulation of integrin $\alpha 5\beta 1$ causes the loss of bone tissue-forming capacity in adipose-derived stromal/stem cells⁸⁰.

Integrin $\alpha 8\beta 1$ binds with TGF- β , tenascin, fibronectin, osteopontin, vitronectin, and nephronectin⁵². It is highly expressed in contractile cells, such as vascular smooth muscle cells, neuronal cells, and mesangial cells⁸¹. Integrin $\alpha 8\beta 1$ functions as a cell migration regulator that promotes or inhibits cell migration according to the differentiated state of cells⁸¹. It promotes the migration of cells that are not initially contractile (such as mesangial cells, vascular smooth muscle cells, and hepatic stellate cells) and inhibits the migration of cells that are differentiated for contractile function (such as neural cells)^{81,82}.

Integrin $\alpha\text{IIb}\beta 3$ is primarily expressed in platelets and their progenitors⁸³. It binds with fibrinogen, fibronectin, thrombospondin, vitronectin, von Willebrand factor, and so on⁵². Integrin $\alpha\text{IIb}\beta 3$ plays a central role in maintaining platelet adhesion, spreading, aggregation, clot retraction, and thrombus consolidation, resulting in platelet activation and arterial thrombosis⁸⁴.

Leukocyte cell adhesion integrins

Leukocytes constitutively express several types of integrins, including $\alpha 4\beta 1$, $\alpha 9\beta 1$, $\alpha\text{L}\beta 2$,

α M β 2, α X β 2, α D β 2, α 4 β 7, and α E β 7⁸⁵(Fig. 3). Among them, integrins containing the β 2 subunit are most abundant in leukocytes; therefore, integrin β 2 is also called a leukocyte integrin⁸⁶.

Leukocyte cell adhesion integrins are primarily involved in the regulation of inflammation. When infection occurs, leukocytes, such as neutrophils, eosinophils, and basophils, are carried close to the site of infection by blood flow^{87,88}. Selectins expressed on leukocytes then bind with their ligands on vascular endothelial cells, which makes leukocytes adhere to the vascular endothelium and start fast rolling⁸⁶. This process provides enough time for integrins to bind with their ligands. Integrins α L β 2 (bound to intercellular adhesion molecule [ICAM]-1), α M β 2 (bound to ICAM-2) and α 4 β 1 (bound to vascular cell adhesion molecule [VCAM]-1) are activated, slowing the rolling of leukocytes⁸⁶. As leukocytes stop in the vascular endothelium, active integrin α L β 2 and α M β 2 induce leukocyte spreading and crawling toward infection⁸⁹. Leukocytes that reach the site of infection cross the vascular endothelium and enter infected tissue with the participation of integrin α 6 β 1, thereby mediating the inflammatory response^{86,89}.

In addition, integrin α L β 2 is also involved in enhancing the phagocytosis of bacteria by neutrophils⁹⁰. It was reported that an integrin α L β 2 antibody effectively inhibited the phagocytosis of *Streptococcus pyogenes* by neutrophils⁹¹. Integrin α M β 2 was proven to be important in neutrophil phagocytosis, reactive oxygen species (ROS) formation, neutrophil extracellular traps (NETs), apoptosis, and cytokine production, thereby regulating inflammation and defending against microbial infection⁹⁰. Integrins α X β 2 and α M β 2 are homologous adhesion receptors that are expressed on similar types of leukocytes and share many receptors⁹². It plays a central role in regulating the anti-inflammatory function of macrophages⁹². Deficiency of integrin α X β 2 results in the loss of antifungal activity of macrophages by eliminating its recruitment and adhesion function⁹² and disturbs dendritic cell recruitment to the infection site⁹³. Integrin α D β 2 is highly homologous to integrin α M β 2 and α X β 2. It binds with ICAM-1, ICAM-3, and VCAM-1, thereby playing an important role in regulating inflammation and microbial infection^{90,94}.

Integrin α E β 7 is mainly expressed in lymphocytes of intestinal, lung and skin epithelial tissues as well as in conventional dendritic cells of mucosa and dermis⁹⁵. The interaction between integrin α E β 7 and E-cadherin mediates lymphocyte attachment to intestinal and skin epithelial cells⁹⁵. In human hematopoietic stem cells and progenitor cells, integrin α 1 β 9 regulates cell adhesion and differentiation in the endosteal stem cell niche, thereby regulating hematopoietic processes⁹⁶. In addition, integrin α 1 β 9 is also involved in the regulation of cell adhesion and migration in numerous organs, such as the skin, liver, and spleen⁹⁷. Integrin α 4 β 7 specifically binds VCAM-1 and mucosal address in cell-adhesion molecule-1 (MAdCAM-1) to regulate lymphocyte migration, which mediates the homing of lymphocytes to gut tissues^{98,99}.

Collagen (GFOGER)-binding integrins

Collagen-binding integrins refer to a class of integrins that bind with GFOGER-like sequences in collagen, including α 1 β 1, α 2 β 1, α 10 β 1, and α 11 β 1¹⁰⁰ (Fig. 3).

Integrin α 1 β 1 was first identified in activated T cells¹⁰¹. It is also expressed in connective tissue cells (such as mesenchymal stem cells and chondrocytes) and cells that are in contact with basement membranes (such as smooth muscle cells, pericytes, and endothelial cells)¹⁰². Integrin α 1 β 1 binds with collagens I, III, IV, IX, XIII, XVI and collagen IV chain-derived peptide arrest^{102,103}. In leukocytes, integrin α 1 β 1 functions as a promoter of T cells in inflammatory responses^{104,105} and mediates monocyte transmigration by binding with collagen XIII¹⁰⁶. In bone, integrin α 1 β 1 plays an important role in damage repair processes. It has been reported that knockout of

integrin $\beta 1$ (ITGB1) results in slowed proliferation of mesenchymal stem cells and inhibition of cartilage production, thereby hindering fracture healing and promoting osteoarthritis^{107,108}.

Integrin $\alpha 2\beta 1$ is expressed in fibroblasts, T cells, myeloid cells, megakaryocytes, platelets, keratinocytes, epithelial cells, and endothelial cells^{100,109}. Integrin $\alpha 2\beta 1$ binds with collagens I, III, IV, V, XI, XVI and XXIII¹⁰⁹. It also binds with lumican and decorin, which are proteoglycans^{110,111}. In platelets, integrin $\alpha 2\beta 1$ participates in stabilizing thrombi by binding with collagen I^{112,113}. In T helper cell 17, integrin $\alpha 2\beta 1$ cooperates with interleukin 7 receptor to mediate bone loss¹¹⁴.

Integrin $\alpha 10\beta 1$ is expressed in fibroblasts, chondrocytes, chondrogenic mesenchymal stem cells and cells lining the endosteum and periosteum¹¹⁵. It primarily binds with collagens II and is essential in cartilage production and skeletal development^{115,116}. Integrin $\alpha 10\beta 1$ is regarded as a biomarker of chondrogenic stem cells¹¹⁵. A previous study revealed that integrin $\alpha 10\beta 1$ deficiency resulted in cartilage defects and chondrodysplasia¹¹⁷.

Integrin $\alpha 11\beta 1$ is expressed in fibroblasts, mesenchymal stem cells, and odontoblasts^{100,118}. It is important in tooth eruption, wound healing, and fibrosis^{119,120}. The osteogenic differentiation of mesenchymal stem cells is driven by integrin $\alpha 11\beta 1$ ¹²¹. Studies have shown that integrin $\alpha 11\beta 1$ deficiency results in incisor tooth eruption defects in mice¹¹⁸. In addition, integrin $\alpha 11\beta 1$ also promotes myofibroblast differentiation, which accelerates dermal wound healing¹¹³. Knockout of integrin $\alpha 11\beta 1$ reduced granulation tissue formation in mice¹²².

Laminin binding integrins

Laminin binding integrins are a group of integrins that bind with laminins¹²³. Laminins are macromolecular glycoproteins located in the ECM¹²⁴. As the main component of the basement membrane, laminins play critical roles in regulating cell adhesion, proliferation, migration, and survival¹²⁵. Laminins consist of various α , β , and γ subunits^{126,127}, which constitute 16 different laminin isoforms^{126,127}.

Integrins that have been identified as binding with laminins include $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 10\beta 1$, $\alpha 6\beta 4$, $\alpha 7\beta 1$, and $\alpha \nu \beta 3$ ¹²⁸⁻¹³⁰ (Fig. 3). Integrins $\alpha 1\beta 1$ and $\alpha 2\beta 1$ bind with the N-terminal domain of laminin $\alpha 1$ and $\alpha 2$ chains¹³¹⁻¹³³. Integrins $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, and $\alpha 7\beta 1$ bind with the C-terminal domain of laminins^{128,134}. Integrin $\alpha \nu \beta 3$ binds with the L4 domain of the laminin $\alpha 5$ chain¹²⁹. However, the physiological effects of the binding of $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 10\beta 1$, and $\alpha \nu \beta 3$ with laminins are very limited, so we generally classify integrins $\alpha 3\beta 1$, $\alpha 6\beta 1$, $\alpha 6\beta 4$, and $\alpha 7\beta 1$ as laminin-binding integrins^{134,135}. Integrins $\alpha 1\beta 1$, $\alpha 2\beta 1$, and $\alpha 10\beta 1$ have been classified as collagen-binding integrins, and integrin $\alpha \nu \beta 3$ has been classified as an RGD-binding integrin (as described above).

Integrin $\alpha 3\beta 1$ is mainly expressed in the lung, stomach, intestine, kidney, bladder, and skin¹²⁵. It mainly binds with laminin-332 and laminin-511 to mediate cell adhesion to the basement membrane and cell-to-cell communication¹²⁵. Studies have found that integrin $\alpha 3\beta 1$ plays a crucial role in the development of the brain, lung, liver, kidney, skin, muscle, and other organs¹³⁶⁻¹⁴⁰. Deficiency in integrin $\alpha 3\beta 1$ causes symptoms such as skin blisters¹⁴¹, disorganization of neurons in the cerebral cortex¹⁴², fragmentation of the glomerular basement membrane¹³⁹, and death in neonatal mice within 24 hours of birth¹³⁹.

Integrin $\alpha 6\beta 1$ is primarily expressed in platelets, leukocytes, gametes, and epithelial cells¹²⁵. Laminin-111, laminin-511 and laminin-332 are the most highly affiliative ligands¹⁴³. In the brain, integrin $\alpha 6\beta 1$ may be involved in nervous system development¹⁴⁴. In the ovary, the interaction of integrin $\alpha 6\beta 1$ with laminins could inhibit progesterone production, thereby regulating luteal formation and follicle growth¹⁴⁵. Moreover, integrin $\alpha 6\beta 1$ in pericytes acts as a regulator of

angiogenesis by controlling the structure of platelet-derived growth factor (PDGF) receptor (PDGFR) β and the basement membrane¹⁴⁶.

Integrin $\alpha 6 \beta 4$ is expressed in subsets of endothelial cells, squamous epithelia, immature thymocytes, Schwann cells, and fibroblasts in the peripheral nervous system^{147,148}. Both laminins and epidermal integral ligand proteins are ligands of integrin $\alpha 6 \beta 4$ ¹²⁵. Integrin $\alpha 6 \beta 4$ binds with laminins and mediates epithelial cell adhesion to the basement membrane, thus maintaining the integrity of epithelial cells¹²⁵. In addition, integrin $\alpha 6 \beta 4$ binds with bullous pemphigoid (BP) antigen 1-e (BPAG1-e) and BP antigen 2 (BPAG2) to form hemidesmosomes (HDs), where the extracellular domain of integrin $\alpha 6 \beta 4$ binds with laminins and the intracellular domain of integrin $\alpha 6 \beta 4$ interacts with the actin cytoskeleton. This structure links the intracellular keratin cytoskeleton to the basement membrane and plays a critical role in regulating the stability of epithelial cell attachment¹⁴⁹⁻¹⁵¹. In mice, integrin $\alpha 6 \beta 4$ deficiency results in reduced skin adhesion properties and extensive exfoliation of epidermal and other squamous cells, accompanied by loss of HDs on the basement membrane of keratinocytes^{147,149}. These findings suggested that integrin $\alpha 6 \beta 4$ might be involved in epidermolysis bullosa^{149,152}. In addition, integrin $\alpha 6 \beta 4$ is also involved in cell death, autophagy, angiogenesis, aging and differentiation regulation and plays a regulatory role in cancer, respiratory diseases, and neurological diseases^{153,154}.

Integrin $\alpha 7 \beta 1$ is mainly expressed in cardiac and skeletal muscles. It binds with laminin-211 and laminin-221 to mediate the binding of muscle fibers with myotendinous junctions. It has been found that integrin $\alpha 7 \beta 1$ deficiency may be one of the important causes of congenital myopathy¹⁵⁵, as integrin $\alpha 7$ (ITGA7) knockout mice develop muscular dystrophy¹⁵⁶. In addition, integrin $\alpha 7 \beta 1$ participates in vascular development and integrity. Studies have revealed that integrin $\alpha 7 \beta 1$ deficiency causes abnormalities in the recruitment and survival of cerebral vascular smooth muscle cells, leading to vascular damage¹⁵⁷.

INTEGRIN-MEDIATED SIGNAL TRANSDUCTION

Inside-out signaling

Integrins act as adhesion and signaling receptors by bidirectionally transducing mechanotransduction and biochemical signals across the plasma membrane, which requires engagement of extracellular ligands by the integrin extracellular domains and recruits additional adaptor, cytoskeletal proteins and signaling molecules to their cytoplasmic tails^{8,158}. The 3D structure of integrins determines their functional state. There are three basic conformations for integrin: a bent conformation, a medium-affinity conformation, and a high-affinity conformation^{8,159} (Fig. 2c). Integrin activity corresponds to the integrin conformation: a bent conformation is associated with a ligand with low affinity, whereas a high affinity is associated with an extended conformation. In the bent conformation, both α and β subunits of the integrin are in a folded state, assuming a compact V-shaped conformation with the headpiece folded over the tailpiece, such that the ligand-binding site of the head is close to the proximal membrane end of both "legs". The affinity of integrin for extracellular ECM and integrin-mediated downstream events are regulated by the dynamic equilibrium between these conformations. The bent conformation is commonly maintained by endogenous inhibitory proteins. For example, Shank-associated RH domain interacting protein (SHARPIN) in leukocytes and mammary-derived growth inhibitor (MDGI) suppress integrin activity by binding directly to the cytoplasmic tail of integrin α -subunit cytoplasmic tails^{160,161}. Additionally, SHARPIN directly binds to integrin $\beta 1$ cytoplasmic tails, and kindlin-1 can significantly enhance this interaction¹⁶². Integrin cytoplasmic associated protein-1 (ICAP1) acts as an inhibitor of $\beta 1$ activation, which can

be antagonized by Krev/Rap1 Interaction Trapped-1 (KRIT1)¹⁶³. Immunoglobulin repeat 21 of filamin A (FLNa-Ig21) not only binds directly to the integrin $\beta 3$ cytoplasmic tail but also interacts with the N-terminal helices of the α IIb and $\beta 3$ cytoplasmic tails to stabilize the bent conformation¹⁶⁴.

In contrast, integrin-binding adaptor proteins inside the cell, including talins (talin 1 and talin 2), kindlins (kindlin 1, kindlin 2 and kindlin 3), vinculin, paxillin, FAK and others binding to the integrin cytoplasmic domain, trigger high-affinity extended integrin conformational changes. The extension of the extracellular domain, the separation of heterodimeric subunits from transmembrane parts in the membrane, and the rearrangement of the $\alpha \beta$ interface in the ligand binding domain release integrins from a compact bent conformation to an open conformation, and the ligand binding affinity increases. Then, integrins may cluster into many different types of adhesive complexes. This activation multi-step process is called activation or inside-out signaling¹⁶⁵, while the signal transmission direction of outside-in is the opposite¹⁶⁶ (Fig. 4). Talin is a main focal adhesion binding protein that initiates inside-out signaling by disrupting the interactions of the α and β subunits, known as the inner membrane clasp¹⁶⁷. The head of talin consists of binding sites for phosphoinositides, rap1 GTPases, F-actin and attach to a rod comprising binding sites for integrin, vinculin, actin, KANK and others, many of which are mechanosensitive and can only be exposed by tensile forces¹⁶⁸. The association of the transmembrane domain (TMD) of α IIb and $\beta 3$ is maintained by specific helical packing TMD interactions near the outer membrane clasp¹⁶⁹, which could be disrupted by talin by altering the topology of the $\beta 3$ TMD^{167,170}. The direct experimental evidence suggested that talin binding to $\beta 3$ -integrin could change the membrane embedding and therefore the topology of integrin $\beta 3$ TMD¹⁷⁰. Proline-induced kink in $\beta 3$ -TMD could break the continuity of the helix and replace the inner membrane clasp interaction¹⁶⁷, which exerts crucial effects on regulating the TMD topography. Similarly, proline-induced kink can also impair talin-mediated $\alpha 4 \beta 7$ activation¹⁷¹. The $\beta 2$ cytoplasmic tail binding to talin-1 can induce a conformational change and result in a change in the angle of the $\beta 2$ TMD, which is further transmitted to the extracellular domain and leads to an extension conformation¹⁷². Recent studies have indicated that introducing the proline mutation L697P kink into the $\beta 2$ TMD can completely affect the change in the extracellular domain of $\beta 2$ conformation and prevent $\beta 2$ integrin extension. Talin-mediated integrin activation is sufficient for inside-out signaling, which could be interfered with by α -actinin in a type-specific way. α -actinin plays opposite roles in controlling the activation of α IIb $\beta 3$ versus $\alpha 5 \beta 1$ integrin by regulating the conformation of TMD¹⁷⁴. It was reported that α -actinin could impair integrin signaling by competing with talin for binding to the $\beta 3$ -integrin cytoplasmic tail and further inducing a kink in the TMD of $\beta 3$ -integrin, whereas it could promote talin binding to $\beta 1$ integrin by restricting cytoplasmic tail movement and reducing the binding entropic barrier¹⁷³. Unlike talin binding to the membrane-proximal NPXY (Asn-Pro-x-Tyr) motif of the β subunit tail, kindlin binds to the membrane distal NXXY motif and facilitates the recruitment of the integrin-linked pseudo kinase-PINCH-parvin complex, paxillin and the Arp2/3 complex to integrins²⁰. Kindlins seem to be regulated by oligomerization but not conformational autoinhibition¹⁷⁴, while vinculin is an autoinhibited adaptor protein with multiple binding sites for other adhesion components, such as talin, IpaA, β -catenin, paxillin, PIP2 and F-actin. Activated vinculin is rapidly recruited to the actin-binding layer from a membrane-apposed integrin signaling layer and recruits additional proteins^{175,176}. Paxillin is a key adaptor protein regulated by phosphorylation, which contains binding sites for adhesion, including parvin, Src, FAK, actopaxin, vinculin, talin, and ILK¹⁷⁷. FAK is a

cytoplasmic tyrosine kinase that is activated by disruption of an autoinhibitory intramolecular interaction and phosphorylates substrates such as paxillin, promoting additional protein docking sites regulating downstream events¹⁷⁸. The “inside-out” pathway receives priming signals from adhesion molecules, chemokine receptors and other intracellular signals. Integrin activation involves various intracellular signaling proteins described above and with other proteins, including spleen tyrosine kinase (SYK), Bruton's tyrosine kinase (BTK), phosphoinositide 3-kinase (PI3K), Rap1-interacting adaptor molecule (RIAM) and associated interacting adapter molecules, allowing subsequent downstream signal transduction¹⁷⁹. For example, in neutrophils, chemokine attachment with G protein-coupled receptors (GPCRs) causes heterotrimeric G-proteins to divide into G_α and $G_{\beta\gamma}$, which initiates phospholipase C (PLC) activation to activate calcium and DAG signals and then promotes PI (4,5) P2 binding to activated RAP1 and RIAM via the PKC-phospholipase D (PLD)-Arf6 axis. This process induces the recruitment of talin-1 and subsequently Kindlin-3 in combination with $\beta 2$ integrin¹⁸⁰. Activated talin is recruited to the cell membrane and binds to induce integrin activation by stimulation with T-cell receptor (TCR) or chemokine receptors, which conduct receptor signaling to downstream cellular events such as migration and chemotaxis¹⁸¹.

Outside-in signaling

Transmembrane connections and mechanotransduction. Cell invasion and migration induced by integrin-mediated adhesion complexes are involved in disease states such as tumor metastasis, autoimmune diseases and other important physiological processes¹⁸²⁻¹⁸⁵. Before adhesion formation, integrins first form tiny clusters at the junction of the cell-ECM. This is sometimes due to the transverse interaction of certain integrins across the membrane domain. These formed and dissolved clusters are regulated by the cell microenvironment¹⁸⁶. Through activation of specific integrin receptors, key adaptor, cytoskeleton and kinase assemble at the cell membrane to form adhesion complexes that transduce signals from the ECM to the interior of the cell. Following integrin activation, the protein complexes consisting of integrin, adaptors, scaffolding molecules, structural proteins, protein kinases, phosphatases, and GTPases are termed IACs^{186,187}. The proteomic differences between active and inactive IACs show a striking 64% similarity¹⁸⁸. Active IACs have stable microtubules that participate in FA disassembly and inhibit their oligomerization. However, inactive IACs have a large number of Ras homology (Rho) and Ras GTPase family proteins, which activate myosin contractility, promoting FA maturation¹⁸⁹. Further analysis identified 60 core proteins in IACs, termed the ‘consensus adhesome’, comprising four potential axes viz. FAK-paxillin, ILK-PINCH-kindlin, α -actinin-zyxin-vasodilator-stimulated phosphoprotein (VASP) and talin-vinculin^{6,22,190,191}. However, Kank2-paxillin and liprin-b1-kindlin have been revealed as new associations. In parallel studies, Kank1 was localized to the periphery of mature IACs by binding talin, coordinating the formation of cortical microtubule stabilization complexes, including ELKS, liprins, kinesin family member 21A (KIF21A), LL5b and cytoplasmic linker-associated proteins (CLASPs), which in turn led to IAC instability^{192,193}. Thus, Kank proteins are also considered possible core adhesome components. IACs are heterogeneous without uniform standard definition. According to size, composition, lifetime, cellular distribution and function, IACs have been classified as nascent adhesions, focal complexes, FAs, invadosomes (podosomes and invadopodia), and reticular adhesions¹⁸⁷. Among them, FAs and FA-like structures are the most representative and well-studied. According to the different stages of cell adhesion to the ECM, classical FAs are preceded by focal complexes and followed by fibrillar adhesions with different molecular compositions¹⁹⁴⁻¹⁹⁶. “Nascent adhesions” or “focal complexes” are the earliest FA-like structures

visible under the light microscope and consist of fewer proteins, such as talin, paxillin, α -actinin and kindlin2, than typical FAs¹⁹⁷. The actin polymerises in nascent adhesions cause retrograde actin flow, starting centripetal from the lamellipodium, which generates force in the opposite direction of the nascent adhesions triggering molecular events involving talin and vinculin that strengthen the integrin-cytoskeleton bonds leading to focal complex formation. This “molecular clutch” is essential for adhesion maturation and eventually cell migration and mechanotransduction¹⁹⁸⁻²⁰¹. It should be noted that although myosin II is not required for the formation of adhesions, its contractility plays an important role in the maturation of the same^{200,202}.

The formation and maturation of FAs require the participation of various proteins in different physiological and pathological contexts. Cooperation between $\alpha v \beta 3$ and $\alpha 5 \beta 1$ integrins has been shown to play a role in FA maturation and cell spreading²⁰³. The binding of Talin to cell membranes has been proven to be essential for integrin activation and FA formation²⁰⁴. Talin, ILK, and the type I γ phosphatidylinositol 4-phosphate [PI(4)P] 5-kinase (PIPKI γ) play a role in polarized FA assembly²⁰⁵. The binding of proteins such as paxillin, vinculin, VASP and zyxin to FAs depends on the orientation and locations of FAs²⁰⁶. This means that FA composition is dynamic, depending on the cellular microenvironment and that many proteins are regulated by the phosphorylation pathway^{189,198,207,208}. As IACs mature, they either disassemble or undergo changes to their protein composition and signaling activity induced by force^{209,210}. In addition to adhesion to ECM ligands, non-ECM ligands or counterreceptors on adjacent cells, integrins serve as transmembrane mechanical junctions that contact the cytoskeleton inside cells from those extracellular²¹¹.

Mechanotransduction is known as the process by which cells sense mechanical stimuli and translate them into biochemical signals and is central to the processes primarily myosin motors, which exert forces on actin filaments anchored to cell-cell or cell-matrix adhesions and mechanosensors. Mechanosensing interacts with tyrosine kinases, and other signaling pathways play a key role in cancer, cardiovascular diseases and other diseases²¹². Integrin-ligand bonds and even all of the above interactions are transient in nature. Some nascent adhesions quickly disperse, while others persist and are trapped in the retrograde actin flow resulting from a combination of actin polymerization, contractile forces applied by myosin II motors and leading-edge membrane tension. Thus, integrin-mediated adhesions link the rearward-flowing actin cytoskeleton to the extracellular environment, allowing cells to exert and experience mechanical forces. This assembly is termed the molecular clutch^{213,214}. The tensile stress caused by actin flow and integrin attachment to the ECM leads to conformational changes that result in exposure of cryptic binding and phosphorylation sites, which allows the recruitment and activation of additional proteins to further regulate downstream signaling pathways²¹⁵. Talin and vinculin are two very important mechanosensitive proteins that regulate the link between integrins and actin. The application of force results in integrin clustering and initiates integrin downstream signaling through the coupling of integrins via talin and vinculin to the actin cytoskeleton. In turn, actin can pull on integrins, further promoting force generation. The N-terminal FERM domain of Talin binds directly to the NPXY motif at the proximal tail membrane of β -integrin. After subsequent attachment to F-actin, talin is stretched to cause a conformational change that exposes the first cryptic vinculin binding site in its rod R3 domain²¹⁶. Vinculin interacts with talin and actin to unfold its closed, autoinhibited conformation²¹⁷, which permits transmission and distribution of mechanical force through the cytoskeleton. Vinculin and talin coordinate to stabilize each other's extended conformational states. Vinculin allows more force to be applied to Talin by linking it to actin, thereby exposing additional

binding sites reciprocally^{216,218}. Among these interactions, the Ras-family small GTPase Rap1 and the Rap1 effector RIAM play a role in recruiting talin to the membrane and facilitating the conformational activation of talin²¹⁹. The Talin rod, rather than vinculin unfolding induced by mechanical force, inhibited the Talin-RIAM interaction, suggesting that force may be a molecular switch regulating the interaction between vinculin-RIAM and talin²²⁰. Additionally, Yes-associated protein 1 (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) signaling has recently been recognized as an important mechanotransducing hub that contributes to integrating cellular and tissue mechanics with metabolic signaling, allowing transcriptional responses²²¹.

Integrin-mediated downstream events. As the transmembrane connection of integrins has been characterized, integrin signaling has been reported to not only modulate IACs formation and actin cytoskeletal rearrangements but also regulate intracellular pathways in response to the ECM or other ECM that triggers “outside-in” signals that serve to modulate gene expression, proliferation, survival/apoptosis, polarity, motility, shape, and differentiation¹⁶⁶. Integrins engage with extracellular activators such as divalent cations, endogenous agonists, activating antibodies, and ligand-mimicking molecules²²²⁻²²⁵, and their subsequent clustering leads to the activation of SYK, FAK and Src family kinases (SFKs), regulating integrin downstream signaling pathways²²⁶. In addition, mechanical forces can also trigger integrin conformational changes downstream^{39,227-230}. Integrin ligation triggers the upregulation of P53 activation, BCL-2 and FLIP prosurvival molecules^{231,232}, and the activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, PI3K/AKT pathway, JNK16 signaling, and stress-activated protein kinase (SAPK) or nuclear factor κ B (NF- κ B) signaling²³³⁻²³⁵. In fibroblasts, integrin-mediated adhesion activates FAK as well as the sodium-proton antiporter and protein kinase C (PKC)²³⁶, and recruitment of FAK to integrins has been considered to precede talin recruitment²³⁷. Integrin-FAK signaling is required for microtubule stabilization²³⁸, leading to anoikis resistance in normal cells and metastasis of independent anchorage growth in tumor cells²³⁹. FAK interacts with a scaffolding protein, and the hematopoietic PBX-interacting protein (HPIP/PBXIP1) in FAs leads to MAPK activation, which leads to Talin proteolysis and contributes to the regulation of cancer cell migration^{187,240-244}. In autosomal dominant polycystic kidney disease, increased ECM fibrosis activates the mechanistic target of rapamycin (mTOR) pathway through the ILK/PINCH/ α Parvin/FAK complex, further accelerating the repair of EMT and cell migration²⁴⁵. The activation of Src family kinases is one of the earliest stages of “outside-in” signaling²⁴⁶. Interaction of integrins with urokinase plasminogen activator receptor (uPAR) activates Rho GTPase to promote cell migration and invasion. α subunit of α v β 3 coupled to Fyn and Yes. Fyn and Yes activate FAK, which is a necessary element in Src homology and collagen homology (SHC) activation. SHC combined with Ras/ERK/MAPK are activated from α v β 3/receptor tyrosine kinase (RTK) receptor combinations, thus activating matrix metalloproteinases (MMPs). Neuropilins (NRPs), vascular endothelial growth factor (VEGF) receptors known as therapeutic targets of tumor growth and metastasis, promote tumorigenesis in breast cancer cells by localizing to FAs and binding to α 6 β 1 integrin to activate FAK/Src²⁴⁷. FAs regulate turnover and cell mobility through microtubules, and autophagy and ubiquitination are equally important for their role as biosensors of the cellular microenvironment and for migration¹⁸⁹. Hypoxia induces anoikis resistance by regulating activating transcription factor 4 (ATF4) and autophagy genes via the integrin signaling pathway. Cell separation from the ECM also triggers integrin signalling via the eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3)-reactive oxygen species (ROS)-ATF4 axis,

promoting autophagy and developing anoikis resistance²⁴⁸. RIAM-VASP relays integrin complement receptors in outside-in signaling driving particle engulfment by determining ERK phosphorylation and its kinetics²⁴⁹. In tandem with the ERK1/2 and c-Jun N-terminal kinase (JNK)1/2 pathways, p1 integrin/FAK/Cortactin pathway signals in FA disassembly and turnover, leading to cell survival and therapeutic drug resistance^{250,251}. Specific mechanical cues, such as rigid environments, lack of spatial constraints and tensile loading, promote YAP/TAZ nuclear translocation and transcriptional activity²⁵². Hippo-YAP signaling depends on the Enigma protein family and FAK, which signal to Hippo through the PI3K pathway²⁵³. Similar to the biophysical cues required for YAP/TAZ activation, myocardin-related transcription factor (MRTF) achieves transcriptional regulation of serum response factor (SRF) by translocating to the nucleus. Mechanistically, MRTFs respond to the G/F-actin ratio because G-actin binds MRTFs to promote nuclear export and sequester the protein in the cytoplasm²⁵⁴. Notably, different integrins regulate downstream signaling pathways through divergent binding mechanisms, such as latent TGF- β (L-TGF- β), a latent form of TGF- β , binding to $\alpha\beta6$ integrin triggers a conformational change from extended-closed to extended open, which allows actin cytoskeletal force to be transmitted through the β subunit to release mature TGF- β from its latent complex²⁵⁵, while the $\alpha\beta8$ has a distinct cytoplasmic domain without interacting with the actin cytoskeleton, and $\alpha\beta8$ -mediated TGF- β activation directs TGF- β signaling to the opposing L-TGF- β /glycoprotein A repetitions predominant (GARP)-expressing cell through the formation of a large multicomponent cell-cell protein complex²⁵⁶. A schematic overview of integrin activation-associated signaling cascades is shown in Fig. 4.

INTEGRIN ROLES IN PHYSIOLOGY AND PATHOLOGY

Integrin roles in cancer

Integrins regulate cell proliferation, adhesion, migration and survival, and tumors can hijack integrin-facilitated biological signaling to participate in every step of cancer progression, including tumor initiation and proliferation, invasiveness, circulating tumor cell survival, metastatic niche formation, immunosuppression, and colonization of the new metastatic site and support multiple therapy resistance²⁵⁷. Integrins are considered therapeutic targets in multiple cancers. The expression of integrins can vary considerably between normal and tumor tissue and is also associated with cancer types and organotrophic metastasis. For example, integrins $\alpha\beta3$, $\alpha\beta6$ and $\alpha5\beta1$ are usually expressed in most normal epithelia at low or undetectable levels but can be highly upregulated in multiple tumors²⁵⁸. The overexpression of the integrins $\alpha\beta3$, $\alpha\beta5$, $\alpha\beta6$, $\alpha5\beta1$, $\alpha6\beta4$, and $\alpha4\beta1$ promotes cancer progression in various cancer types. The expression and function of major integrins and their related cancer types and metastatic sites are shown in Fig. 5, which indicates the applicability of these integrin receptors as therapeutic targets and underlines the requirement for patient stratification in future clinical studies. Herein, we summarize the recent progress in the engagements of integrins and integrin-regulated mechanisms in different cancers.

Integrin and tumorigenesis. Most integrins act as tumorigenesis promoters in multiple solid tumors, but some integrins also act as suppressors in tumor tumorigenesis²⁵⁷. The $\beta1$ integrin family has heterogeneity in tumor initiation and progression^{259,260}. Several studies have suggested a beneficial role for the inhibition of $\beta1$ integrin or deletion of the $\beta1$ gene, including reversal of the malignant phenotype in breast cancer and reduction of drug resistance and metastasis in gastric, ovarian, and lung cancer²⁶¹⁻²⁶⁴. $\alpha2\beta1$ integrin is highly expressed on normal breast epithelium, and $\alpha2\beta1$ integrin is reported to be a metastasis suppressor in mouse models and human breast cancer

¹²⁵. Other studies, however, suggested integrin $\alpha 2$ or $\alpha 2\beta 1$ as a key regulator of hepatocarcinoma cell invasion and conferring selective potential for the formation of hepatic metastasis ²⁶⁵. In addition, many studies have also proven that laminin-binding integrins ($\alpha 3\beta 1$ and $\alpha 6\beta 4$) exert opposing effects (tumor-promoting and suppressive) on tumor development and progression ¹²⁵. Integrins may act as tumor suppressors by activating TGF- β and exerting anti-proliferative effects in the early stage of tumor formation until the cancer becomes refractory, and the inhibitory effect of TGF- β on tumor cell proliferation will decrease or even disappear; then, the same integrins can drive tumor progression ^{266,267}. $\beta 1$ integrin expression and function are associated with metabolic reprogramming. An array of studies has suggested that glycolytic enzymes affect $\beta 1$ integrin expression, which produces a vicious cycle for promoting cancer progression ²⁶⁸. In colon cancer cells, the glycolytic enzyme pyruvate kinase M2 induces metabolic reprogramming, positively affecting the overexpression of enhanced $\beta 1$ integrin expression and increasing cell migration and adhesion ²⁶⁹. Inhibition of glycolytic enzymes could decrease integrin $\beta 1$ expression and proliferation in breast cancer cells ^{268,269}.

Integrins also play an important role in regulating immune response during tumor development ²⁷⁰. Importantly, as a gut-tropic molecule, integrin $\alpha 4\beta 7$ plays a profound role in regulating the progression of colorectal cancer (CRC) ²⁷¹. $\alpha 4\beta 7$ mediates the recruitment of IFN- γ -producing CD4⁺ T cells, cytotoxic CD8⁺ T cells, and NK cells to the CRC tissue where they exert effective anti-tumor immune responses ²⁷¹. Higher $\beta 7$ expression levels are correlated with longer patient survival, higher cytotoxic immune cell infiltration, lower somatic copy number alterations, decreased mutation frequency of APC and TP53, and better response to immunotherapy ²⁷¹.

Integrins have been reported to sustain intratumoral cancer stem cell (CSC) populations depending on tumor type. Prospective identification studies suggested that integrin $\alpha \nu \beta 3$, $\alpha 6\beta 1$ and $\alpha 6\beta 4$, which are overexpressed in CSCs, promote the sustainability of self-renewal and the expansion of CSCs for tumor initiation ²⁷². Actually, the $\alpha 6$ and $\beta 3$ subunits are regarded as a signature of luminal precursor cells in mammary ductal epithelium ²⁷³, and the $\alpha 6$ and $\beta 4$ subunits are generally applied as markers to identify bipotential progenitors in normal prostate and prostate cancer in mice ^{274,275}. Deletion of the signaling domain of $\beta 4$, which also pairs with $\alpha 6$, decreases the self-renewal ability of prostate tumor progenitors ²⁷⁵.

Integrins play key regulatory roles in neovascularization. Endothelial cells highly express a diverse repertoire of $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha \nu \beta 3$, $\alpha 5\beta 1$ and $\alpha \nu \beta 5$ ^{276,277}. In particular, $\alpha \nu \beta 3$ is expressed on quiescent endothelial cells at very low levels but is markedly increased during tumor angiogenesis ²⁷⁸. Therefore, integrin $\alpha \nu \beta 3$ antagonists can induce endothelial cell apoptosis in neovasculature without affecting the normal vasculature, which leads to many peptide-based integrin inhibitors and antibodies developed in clinical trials for cancer treatment. Integrin $\alpha \nu \beta 3$ and VEGF have a synergistic signaling connection during the activation of endothelial cells and vascularization induced by interplay between VEGF and ECM molecules ²⁷⁹. The anti-integrin $\alpha \nu \beta 3$ antibody BV4 inhibits the phosphorylation of VEGFR2 ²⁷⁹, and the VEGFR2-specific inhibitor SU1498 inhibits the complex interaction between VEGFR2 and integrin $\beta 3$ ²⁸⁰. FAK-Src signaling is important in both $\alpha \nu \beta 3$ and VEGF-associated tumor angiogenesis ²⁴³. The crosstalk of integrin $\alpha \nu \beta 3$ and VEGFR2 could be regulated by Src. Src inhibitors not only block both the phosphorylation of integrin and VEGFR2 but also complex formation between VEGFR2 and integrin $\beta 3$ ²⁸¹. The interplay of integrin $\alpha \nu \beta 3$ in VEGFR signaling should be considered in anti-angiogenesis drug development.

Integrin and metastatic cascade. Metastasis causes 90% of cancer deaths²⁸². The “seed-and-soil” hypothesis provides insight into organ-specific metastasis. Integrins engage in the metastatic cascade, which is dependent on tumor type, stage, metastatic site, and microenvironmental influences. For breast, prostate and lung malignancies, the most frequent metastasis site is bone. The correlative evidence suggests that the role of integrins (e.g., $\alpha\text{v}\beta3$, $\alpha2\beta1$, $\alpha4\beta1$, $\alpha5\beta1$) mediates the interactions of tumor cells with the bone microenvironment. $\alpha\text{v}\beta3$ has been studied most as an important integrin for bone metastasis²⁸³. Integrin $\alpha\text{v}\beta3$ was expressed at higher levels in breast cancer patients with bone metastases than in their primary tumors²⁸⁴. Tumor-specific $\alpha\text{v}\beta3$ participates in breast cancer spontaneous metastasis to bone by mediating chemotactic and haptotactic migration towards bone factor²⁸⁵. Functional modulation of $\alpha\text{v}\beta3$ is also required for prostate cancer within bone metastasis and for tumor-induced bone gain²⁸⁶. In addition, $\alpha\text{v}\beta3$ activation depends on the recognition of specific bone-specific matrix ligands²⁸⁶. $\alpha\text{v}\beta3$ could be a potential marker for bone metastasis, and treatment with $\alpha\text{v}\beta3$ antagonists can reduce the capacity of tumor cells to colonize bone²⁸⁷.

In recent years, exosomes have been recognized as the “primers” of the metastatic niche²⁸⁸. Integrins, as the most highly expressed receptors on exosomes, are major players in mediating exosome functions and especially exert important effort in guiding exosomes to spread into the prime long-distance organs to form a premetastatic niche and further support organ-specific metastasis²⁸⁹. A comprehensive proteomic investigation suggested diverse exosome-carrying integrins derived from different types of primary tumors²⁹⁰. Most notably, lung-tropic cancer cells predominantly secreted $\alpha6\beta1$ integrins and $\alpha6\beta4$ integrin-positive exosomes, while liver-tropic cancer cells mainly shed exosomes with a high enrichment of $\alpha\text{v}\beta5$ integrin²⁹⁰. Targeting exosome uptake of integrins $\alpha6\beta4$ and $\alpha\text{v}\beta5$ can reduce lung and liver metastasis, respectively²⁹⁰. In prostate cancer, $\alpha\text{v}\beta6$ is not detectable in the normal human prostate but is highly expressed in primary prostate cancer²⁹¹. It was reported that $\alpha\text{v}\beta6$ is packaged into exosomes secreted by prostate cancer cells and transferred into $\alpha\text{v}\beta6$ -negative recipient cells, which contributes to enhancing cell migration and metastasis in a paracrine fashion²⁹¹. $\alpha\text{v}\beta3$ -expressing exosomes are highly enriched in the plasma of prostate cancer patients; in addition, the levels of $\alpha\text{v}\beta3$ remain unaltered in exosomes isolated from blood from prostate cancer patients treated with enzalutamide²⁹². Exosome-carrying integrin $\alpha\text{v}\beta3$ is transferred to nontumorigenic recipient cells and promotes a migratory phenotype²⁹³. Exosome-carrying integrin $\alpha3$ (ITGA3) and ITGB1 from urine from prostate cancer with metastasis are more abundant than those from benign prostate hyperplasia or primary prostate cancer²⁹⁴. In pancreatic cancer, numerous lines of evidence suggest that exosomal integrins also play key roles in exosome-mediated tumor progression and metastasis; for example, exosome-carrying $\alpha\text{v}\beta5$ released by primary tumor cells in the pancreas tends to metastasize to the liver, whereas $\alpha6\beta4$ and $\alpha6\beta1$ tend to metastasize to the lung²⁹⁵. In future studies, the general applicability of exosome integrin-mediated organ-specific metastasis remains to be validated *in vivo* models and in other cancer types.

Integrin and drug resistance. Tumor metastasis and therapeutic resistance together determine a fatal outcome of cancer. Interactions between cell surface integrins and ECM components have been found to be responsible for intrinsic and acquired therapy resistance, which is named cell adhesion-mediated drug resistance (CAMDR)^{282,288}. Generally, integrins are involved in resistance to most first-line therapies in the clinic, such as radiotherapy²⁸⁹, chemotherapy²⁹⁰, angiogenesis²⁹¹, endocrine therapy²⁹², and immunotherapy²⁹³. The mechanism of integrin-induced primary and

adaptive drug resistance is variegated. In various cancers, $\beta 1$ integrin-interacting matrix molecules promote primary radiotherapy resistance by activating DNA repair and prosurvival signaling through the engagement of FAK, SRC, PI3K-AKT and MAPK signaling²⁹⁴⁻²⁹⁷. In addition, integrin-mediated reprogramming also induces radiosensitization²⁸⁹. The interaction of Integrin with ECM by activating ATP binding cassette (ABC) efflux transporters enhances the intracellular drug concentration and promotes chemoresistance to doxorubicin and mitoxantrone²⁹⁸. Cluster of differentiation-44 (CD44), alone or together with MET receptor, also participates in the upregulation of P-glycoprotein (P-gp) expression and promotes chemoresistance²⁹⁹. In xenograft models and patient specimens, Arman et al. found that c-Met replaced $\alpha 5$ integrin from $\beta 1$ integrin and formed the c-Met/ $\beta 1$ complex during metastases and invasive resistance, and decoupling the crosstalk in the c-Met/ $\beta 1$ complex may have therapeutic implications for antiangiogenic drug resistance³⁰⁰. The interaction of integrin $\alpha \beta 3$ with osteopontin engages in acquired epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) resistance by activating the downstream FAK/AKT and ERK signaling pathways in EGFR mutant non-small cell lung cancer³⁰¹. Integrins are involved in invasion, angiogenesis, bone metastases and anti-androgen resistance in prostate cancer²⁹². The mechanism of resistance to androgen ablation is not well understood. In our previous study, we found that the integrin-ECM interaction promotes enzalutamide (anti-androgen drug) resistance in castration-resistant prostate cancer (CRPC) via the PI3K/AKT and ERK1/2 pathways³⁰². $\alpha \beta 3$ and $\alpha \beta 6$ expression are required for prostate cancer progression, including CRPC. Integrin $\alpha \beta 6$ can induce androgen receptor (AR)-increased activity in the absence of androgen via activation of JNK1 and further upregulation of survival³⁰³. In mouse melanoma and breast cancer models, Tregs expressing integrin $\beta 8$ (ITGB8) are the main cell type in the tumor microenvironment, which activates TGF- β produced by cancer cells and promotes immune escape, and ITGB8 ablation or anti-ITGB8 antibody treatment could improve cytotoxic T-cell activation²⁹³. In triple-negative breast cancer (TNBC), integrin $\alpha \beta 6$ on the surface of tumor cells activates TGF- β , and upregulating SRY-related HMG box (SOX) 4 transcription factor contributes to immunotherapy resistance. An integrin $\alpha \beta 6/8$ -blocking monoclonal antibody can inhibit SOX4 expression and sensitize TNBC cells to programmed cell death ligand 1 (PD-1) blockade³⁰⁴. Therefore, targeting integrin is regarded as a promising therapeutic opportunity for overcoming multiple drug resistance.

Integrin roles in fibrotic diseases

Fibrosis refers to chronic inflammation or injury induced by various factors, resulting in an increase in fibrous connective tissue and a decrease in parenchymal cells. It causes abnormal structural changes and functional abnormalities in injured organs, which is an abnormal manifestation of excessive damage repair³⁰⁵. Fibrosis occurs in almost any organ, especially the liver, lung, and kidney. Fibrosis diseases are difficult to detect in the early stages, and most are found to have progressed to organ sclerosis, which can be life-threatening for patients³⁰⁵. Currently, therapies for fibrosis disease are still limited, and organ transplantation is the only effective treatment option for end-stage fibrosis diseases³⁰⁶. However, due to the limited number of donor organs and their high price, replacement therapy has not been widely used. It is particularly important to develop new antifibrotic drugs from the pathogenesis of fibrosis.

TGF- $\beta 1$ plays a critical role in the pathogenesis of fibrosis and has been considered a therapeutic target for fibrotic diseases³⁰⁷⁻³⁰⁹. Unfortunately, both preclinical and clinical trials have shown that direct targeting of TGF- $\beta 1$ for fibrosis disease treatment is not feasible³⁰⁸. TGF- $\beta 1$ is involved in the regulation of the immune system and plays important anticancer and cardiac function

716 maintenance roles^{308,310,311}. Global inhibition of TGF- β 1 leads to serious multiple organ dysfunction
717³⁰⁸.

718 Encouragingly, researchers have found that blocking the interaction between integrins
719 (especially integrins rich in α v subunits) and TGF- β 1 showed an efficient anti-fibrosis effect without
720 causing TGF- β 1 dysfunction-induced adverse effects³⁰⁵. Integrins are receptors by which cells
721 adhere to the ECM³¹². Several integrins have been confirmed as activators of TGF- β 1³¹², and
722 antagonists of α v β 1⁵⁴ and α v β 6^{313,314} have shown considerable inhibitory effects in experimental
723 animal models of liver, lung, and renal fibrosis. In fact, in recent years, several integrin inhibitors
724 have been developed and evaluated in phase II and III clinical trials in fibrotic diseases, such as
725 PLN-74809, IDL-2965, GSK3008348, and STX-100³¹⁵. These findings revealed the promise of
726 integrin inhibitors in the treatment of fibrotic diseases. In the following, we focus on nonalcoholic
727 steatohepatitis (NASH), pulmonary hypertension (PH), and autosomal dominant polycystic kidney
728 disease (ADPKD), the diseases that usually cause fibrosis, and discuss the role of integrins in
729 fibrotic processes (Fig. 6).

730 **NASH.** NASH, a chronic liver disease that develops from nonalcoholic fatty liver disease (NAFLD),
731 is one of the most common chronic liver diseases in patients without a history of alcohol abuse
732^{316,317}. Approximately 30~40% of NASH patients develop fibrosis, and 10% develop cirrhosis³¹⁸.
733 The prognosis of NASH depends on histological severity, especially hepatic fibrosis³¹⁹. Therefore,
734 preventing the progression of NASH to liver fibrosis is of great importance in NASH treatment.
735 Despite the increasing incidence of NASH-related liver fibrosis, which currently kills 2 million
736 people worldwide each year³²⁰⁻³²², there are no approved drugs. Most drugs in clinical trials target
737 the early stages of steatosis/hepatitis other than fibrosis itself, which generally result in inadequate
738 outcomes^{323,324}. This dilemma provides an opportunity for integrin inhibitors to be applied in the
739 treatment of liver fibrosis²⁸. Several integrins have been identified to inhibit the progression of
740 NASH to liver fibrosis, including α v β 3, α 4 β 7, α 9 β 1, and α 8 β 1 (Fig. 6).

741 Integrin α v β 3 is expressed in hepatic stellate cells (HSCs)³²⁵, which are considered key
742 mediators of fibrotic responses³²⁶. Generally, integrin α v β 3 induces myofibroblast cells to express
743 α -smooth muscle actin (α -SMA), leading to excessive production of ECM^{327,328}. It has been
744 reported that integrin α v β 3 and α v β 5 bind with secreted osteopontin in the liver of NAFLD mice,
745 which inhibits autophagosome-lysosome fusion and promotes lipid accumulation³²⁹. Application
746 of osteopontin antibody not only suppressed hepatic steatosis but also attenuated liver fibrosis³²⁹,
747 indicating a functional role of integrin α v β 3 and α v β 5 in inhibiting the progression of NASH to liver
748 fibrosis. Moreover, in high glucose-induced human liver sinusoidal endothelial cells (HSECs) (an
749 *in vitro* model of NAFLD), integrin α v β 3 antibody (clone LM609) significantly downregulated the
750 expression of laminin and suppressed fibrosis³³⁰. In fact, numerous studies have confirmed the
751 efficacy of integrin α v β 3 as a predictor of fibrosis in experimental NASH models^{325,328,331}. However,
752 no integrin α v β 3 inhibitors have been evaluated in clinical trials to investigate their inhibitory effect
753 on the progression of NASH to liver fibrosis. It is waiting to be explored.

754 Integrin β 7 expressed in leukocytes is regarded as an important receptor that binds to
755 MAdCAM-1 and induces homing of leukocytes to gut-associated lymphoid tissue³³². Integrin β 7
756 pairs with other integrin α subunits, including α 4 and α E³³², in which α 4 β 7 affects the progression
757 of NASH to liver fibrosis³³²⁻³³⁴. At first, researchers focused only on the role of integrin β 7 in
758 NASH-induced liver fibrosis. Knockout of integrin β 7 (ITGB7) significantly promoted
759 inflammatory cell infiltration and fibrosis in the livers of NASH mice³³². In contrast, MAdCAM-1

knockout showed anti-inflammatory activity³³². Later, integrin $\alpha 4 \beta 7$ was found to play an important role in the progression of NASH to liver fibrosis. The abnormality of gut microbiota in NASH mouse models promoted the expression of MADCAM-1 in the liver, which recruited $\alpha 4 \beta 7$ -positive CD4 T cells to the liver and induced inflammation and fibrosis³³⁴. Blocking integrin $\alpha 4 \beta 7$ has shown promising therapeutic effects on fibrosis in NASH³³⁴, indicating its great potential as a therapeutic target for NASH-induced liver fibrosis.

Integrin $\alpha 9 \beta 1$ plays an important role in lipotoxic hepatocyte-induced hepatic recruitment of monocyte-derived macrophages (MoMFs), which promotes the progression of NASH to fibrosis³³⁵. Integrin $\alpha 9 \beta 1$ expressed in hepatocytes could be activated by hepatocyte lipotoxicity and endocytosed by hepatocytes³³⁵. Extracellular vesicles are formed and secreted by hepatocytes, which are further captured by MoMFs³³⁵. Integrin $\alpha 9 \beta 1$ mediates MoMF adhesion to liver sinusoidal endothelial cells by binding to VCAM-1, which induces inflammation³³⁵. Blocking integrin $\alpha 9 \beta 1$ significantly reduced liver injury, liver inflammation, and liver fibrosis³³⁵, indicating that it is a therapeutic target for fibrosis in NASH. In addition, it has also been reported that anti-mouse osteopontin mouse IgG (35B6) inhibits the cell adhesion of mouse and human osteopontin to Chinese hamster ovary (CHO) cells expressing integrin $\alpha 9$, which suppresses liver inflammation and fibrosis in NASH mice³³⁶. All these findings revealed the therapeutic potential of integrin $\alpha 9 \beta 1$ inhibitors in liver fibrosis induced by NASH.

Integrin $\alpha 8 \beta 1$ is expressed in smooth muscle cells, HSCs, and fibroblasts³³⁷. It was upregulated in patients with NAFLD and liver fibrosis^{82,338}. In NASH, the activation of HSCs expressing the integrin $\alpha 8$ subunit has been proven to be an agonist of latent TGF- β , which participates in promoting fibrosis⁸². A previous study showed that inhibiting the integrin $\alpha 8$ subunit with an integrin $\alpha 8$ antibody significantly improved liver fibrosis in a NASH mouse model⁸². In addition, miR-125b-5p silencing caused by NAFLD also downregulated integrin $\alpha 8$, which inhibited the RhoA signaling pathway and promoted fibrosis³³⁸. These results implied the functional role of integrin $\alpha 8 \beta 1$ in promoting liver fibrosis induced by NASH.

Moreover, other integrins have also been proven to be involved in liver fibrosis. Integrins containing the αv subunit have received the most attention due to their activating activity on TGF- β , including $\alpha v \beta 1$, $\alpha v \beta 5$, $\alpha v \beta 6$, and $\alpha v \beta 8$ ^{306,327}. In addition, integrins $\alpha 11$ and RGD-recognizing integrins (such as $\alpha 11 \beta 3$ and $\alpha 5 \beta 1$) are also important regulators of liver fibrosis³³⁹. Integrin inhibitors such as IDL-2965 and PLN-74809 have been investigated in clinical trials to evaluate their therapeutic effect on liver fibrosis³³⁹. However, none of their roles in fibrosis induced by NASH have been elucidated. It may be a promising direction for the treatment of NASH-derived liver fibrosis.

PH. PH is a disorder of the pulmonary vasculature defined by increased pulmonary vascular resistance ≥ 3 Wood units³⁴⁰. It is characterized by excessive pulmonary vasoconstriction and vascular remodelling resulting in persistent elevation of pulmonary arterial pressure³⁴¹. PH causes right ventricular hypertrophy, right heart dysfunction, and even right heart failure, threatening up to 100 million people worldwide^{340,342}. Pulmonary vascular remodelling in PH involves the processes of endothelial injury, endothelial cell abnormality, excessive vascular smooth muscle cell proliferation, invasion of the intima by (myo)fibroblast-like cells and, especially, intimal fibrosis³⁴³. Increased deposition of interstitial ECM components, including collagen, elastin, tenonin-C, and fibronectin, has been demonstrated in human patients and animal models^{341,344-346}. As the receptor for ECM proteins, integrins play important roles in maintaining vascular remodelling³⁴⁷.

Pulmonary vasculature expresses several types of integrins, including $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\alpha 7$, $\alpha 8$, $\alpha \nu$, $\beta 1$, $\beta 3$, and $\beta 4$ ^{12,348,349} (Fig. 6). Studies revealed that in the pulmonary arteries (PAs) of chronic hypoxia and monocrotaline-treated PH rat models, integrin $\alpha 1$, $\alpha 8$, and $\alpha \nu$ were upregulated, and integrin $\alpha 5$, $\beta 1$, and $\beta 3$ were downregulated significantly^{347,350}. Integrin $\alpha \nu$ activates TGF- $\beta 1$ and TGF- $\beta 3$, which are critical to vascular homeostasis. TGF- β regulates PH through multiple signalling pathways, including upregulation of endothelial nitric oxide synthase, stimulation of VEGF and endothelin-1, alteration of bone morphogenetic protein (BMP) signalling, and anaplastic lymphoma kinase (ALK)-1–ALK-5 signalling in endothelial cells^{351–353}. Integrins $\beta 1$ and $\beta 3$ have been reported to regulate cell proliferation by interacting with activated ILK, a pro-proliferative protein kinase. ILK is activated by integrins in response to growth factors and cytokines, which in turn trigger downstream signals, including activation of Akt and inhibition of the growth suppressor HIPPO^{354–356}. ILK1 is upregulated in pulmonary artery vascular smooth muscle cells (PAVSMCs) of human pulmonary arterial hypertension (PAH) and experimental models and is required for increased cell proliferation, survival, pulmonary vascular remodelling, and overall PH, and inhibition of ILK reverses experimental PH in male mice³⁵⁵. Researchers believe that integrin $\alpha 1$ and $\alpha 5$ may participate in regulating ECM, as they are expressed in the smooth muscle cells of PAs (PASMCs)³⁴⁷. In these processes, integrin $\alpha 1$ -ligand collagen IV expands, while integrin $\alpha 5$ -ligand fibronectin suppresses chronic hypoxia treatment-induced FAK phosphorylation³⁴⁷. The regulatory effects of integrin $\alpha 1$ and $\alpha 5$ on FAK phosphorylation then react to Ca^{2+} signaling, which may be involved in intimal fibrosis³⁴⁷.

In addition, integrin $\beta 3$ may function as an inhibitor of fibrosis and vascular remodelling in PH. It has been reported that silencing integrin $\beta 3$ (ITGB3) significantly improves chronic hypoxia-induced pulmonary hemorrhage, pulmonary vascular remodelling, and pulmonary fibrosis in rats³⁵⁰. These effects may come from the interaction between integrin $\beta 3$ and ECM. However, the underlying mechanism still needs to be clarified. The role of integrin $\alpha \nu$ in regulating PH-induced fibrosis has attracted little attention. However, the interaction between $\alpha \nu \beta 3$ and osteopontin has been confirmed, which activates FAK and AKT, promoting the proliferation of PASMCs and enhancing vascular remodelling^{357,358}.

ADPKD. ADPKD is an autosomal dominant kidney disease caused by polycystic kidney disease-1 (PKD1) or polycystic kidney disease-2 (PKD2) gene mutations. It is the fourth leading cause of end-stage renal disease (ESRD), with an incidence of approximately 1/2500 to 1/1000^{359,360}.

ADPKD is characterized by progressive growth of multiple renal tubules and collecting duct-derived cysts in bilateral kidneys, which compress the renal parenchyma and cause nephron loss³⁶¹. Fibrosis is an important pathophysiological change of ADPKD that directly leads to renal dysfunction and induces ESRD³⁵⁹. Therefore, antifibrosis is important in the treatment of ADPKD. However, apart from replacement therapies, there is no clinical solution that could effectively prolong the lifespan of ADPKD patients, which makes it urgent to develop new drugs³⁶².

In recent decades, research on integrin function in fibrotic kidney diseases has achieved exciting results. A growing number of integrins have been found to play regulatory roles in the progression of fibrosis in renal dysfunction and show great potential as therapeutic targets for renal disease. In particular, integrin $\alpha \nu \beta 3$ ²⁴⁵ and $\beta 1$ ³⁶³ are promising antifibrotic targets in ADPKD treatment (Fig. 6).

As an important activator of latent TGF- $\beta 1$, integrin $\alpha \nu \beta 3$ enhances TGF- β /small mothers against decapentaplegic (SMAD) signaling pathways, which induces ECM production, promoting

renal fibrosis in ADPKD²⁴⁵. Periostin is a ligand of integrin $\alpha\text{v}\beta 3$, which binds to integrin $\alpha\text{v}\beta 3$ through its fasciclin 1 (FAS1) domains and promotes the release of TGF- β from latent TGF- β -binding protein²⁴⁵. Periostin (Postn) has been confirmed as a profibrotic factor and was upregulated in ADPKD³⁶⁴. Studies reported that global knockout of postn in pcy/pcy mice, an ADPKD mouse model, significantly inhibited renal cyst development and renal fibrosis³⁶⁵. In contrast, overexpression of periostin obtained the opposite results³⁶⁶. All these effects of periostin on fibrosis in ADPKD were thought to be mediated by integrin $\alpha\text{v}\beta 3$ ³⁶⁴⁻³⁶⁶. Recently, osteopontin was reported as a urinary biomarker for predicting ADPKD progression³⁶⁷. Since osteopontin is another ligand that activates the interaction between integrin $\alpha\text{v}\beta 3$ and TGF- $\beta 1$, this study seems to confirm the profibrotic effects of integrin $\alpha\text{v}\beta 3$ in ADPKD.

Integrin $\beta 1$ is the most prevalent β -chain integrin subunit expressed in the kidney³⁶⁸. It has been reported that knockout of ITGB1 significantly ameliorates renal fibrosis by suppressing the expression of α -smooth muscle actin (α -SMA), fibronectin, and collagen in the kidneys of PKD1 knockout mice³⁶³. Several integrins that contain the $\beta 1$ subunit have been identified as regulators of renal fibrosis, including $\alpha 1\beta 1$ ³⁶⁹, $\alpha 2\beta 1$ ³⁷⁰, $\alpha 5\beta 1$ ³⁷¹, and $\alpha\text{v}\beta 1$ ³⁷². Although whether these integrins function in the fibrotic process of ADPKD has not been fully elucidated, their great potential to be developed as an antifibrotic target for ADPKD treatment could not be neglected.

In addition, integrins contain αv subunits (such as $\alpha\text{v}\beta 5$ ³⁷³ and $\alpha\text{v}\beta 6$ ³⁷⁴), and integrin $\alpha 3$ ³⁷⁵ also participates in promoting renal fibrosis. However, the roles they play in ADPKD are unclear. However, there is no integrin inhibitor that undergoes a clinical trial to evaluate its therapeutic effects on renal fibrosis. In future studies, the profibrotic mechanism of integrins in ADPKD and evaluating their therapeutic effect on ADPKD are expected to disperse the dimness brought by ADPKD.

Integrin roles in cardiovascular diseases

Atherosclerosis. Atherosclerosis (AS) is the fundamental pathological process of vascular diseases. The rupture of atherosclerotic plaques and secondary thrombosis are the most common causes of severe vascular events. The alteration of integrin signaling pathways can affect multiple aspects of AS, such as endothelial dysfunction and activation, leukocyte homing to the plaque, leukocyte function within the plaque, smooth muscle recruitment and fibroproliferative remodelling, and thrombosis³⁷⁶. In view of the crucial role of integrins in the occurrence and development of AS, we review the integrin regulation of AS and the potential of integrins as therapeutic targets. The model for atherosclerotic plaque development and the main roles of integrins in the process of AS are shown in Fig. 7.

Oxidized low-density lipoproteins (Ox-LDL) and shear stress generated by blood flow lead to endothelial cell dysfunction, which in turn promotes inflammatory cell homing and infiltration. Monocytes migrate into the subendothelium, transform into macrophages and initiate AS. Ox-LDL can activate $\alpha 5\beta 1$ and induce $\alpha 5\beta 1$ -dependent signal transduction, thereby activating the FAK/ERK/p90 ribosomal S6-kinase (p90RSK) pathway to induce NF- κB signaling³⁷⁷. Shear stress activates provisional matrix binding integrins ($\alpha 5\beta 1$ and $\alpha\text{v}\beta 3$), and some studies have reported that $\alpha\text{v}\beta 3$ inhibition is sufficient to prevent NF- κB activation involving p21-activated kinase (PAK) signaling on fibronectin^{378,379}. In addition, proinflammatory gene expression (ICAM-1 and VCAM-1) also increases after ox-LDL and shear stress-induced ligation of provisional matrix-binding integrins^{377,380}.

Leukocytes express integrins that mediate interactions with cell adhesion molecules on endothelial cells. Several studies have shown that $\alpha 4 \beta 1$ and various $\beta 2$ integrins play vital roles in the formation of atherosclerotic plaques. $\alpha 4 \beta 1$ is the major leukocyte VCAM1 receptor³⁸¹. $\alpha x \beta 2$ and $\alpha 4 \beta 1$ can bind VCAM-1 cooperatively to promote leukocyte adhesion³⁸². In addition, $\alpha x \beta 2$ and $\alpha L \beta 2$ interact with ICAM1/2 on the surface of endothelial cells. Deficiency of αx integrin significantly reduces monocyte recruitment and AS development in apoE^{-/-} hypercholesterolemic mice³⁸³. Monocyte integrins $\alpha 4 \beta 1$, $\alpha 9 \beta 1$, and $\alpha v \beta 3$ interact with osteopontin, which is expressed in atherosclerotic plaques, to promote monocyte migration and survival³⁸⁴. Integrin $\alpha D \beta 2$ shows prominent upregulation during macrophage foam cell formation³⁸⁵. Meanwhile, ligation of specific macrophage integrins (e.g., $\alpha M \beta 2$, $\alpha v \beta 3$) may affect various aspects of macrophage function in AS³⁷⁶, including macrophage clearance of local lipid deposits³⁸⁶⁻³⁸⁸, phagocytosis of apoptotic cell debris^{389,390} and the ability to promote local proinflammatory gene expression³⁹¹. Recently, nexinib20, a neutrophil exocytosis inhibitor, has been confirmed to inhibit exocytosis and neutrophil adhesion by limiting $\beta 2$ activation³⁹², which sheds new light on targeting integrin $\beta 2$ therapy.

Vascular smooth muscle cells (VSMCs) are vital in the progression of AS because they can transdifferentiate into proliferative and migratory phenotypes. Current studies support the key role of $\alpha v \beta 3$ signaling in smooth muscle proliferation and migration. Both $\alpha 5 \beta 1$ and $\alpha v \beta 3$ bind to fibronectin, and their inhibitors reduce atherosclerotic plaque formation, but only $\alpha v \beta 3$ inhibition reduces fibrous cap formation incidence^{378,393}. Ligation of $\alpha v \beta 3$ and $\alpha v \beta 5$ integrins mediates FAK activity³⁹⁴ and causes VSMC migration by AKT and paxillin phosphorylation³⁹⁵⁻³⁹⁷.

The rupture of an atherosclerotic plaque is the primary trigger for arterial thrombosis. Platelets express integrins of the $\beta 1$ and $\beta 3$ families ($\alpha 2 \beta 1$, $\alpha 5 \beta 1$, $\alpha 6 \beta 1$, $\alpha v \beta 3$, and $\alpha IIb \beta 3$), whose main ligands are collagen, fibronectin, laminins, vitronectin, and fibrinogen, respectively³⁹⁸. Platelet adhesion promoted by $\alpha 2 \beta 1$ induces $\alpha IIb \beta 3$ activation by the phospholipase C-dependent stimulation of the small GTPase Rap1b³⁹⁹. Inactive $\alpha IIb \beta 3$ on resting platelets is conformationally converted into active to bind fibrinogen, triggering platelet aggregation and augmenting thrombus growth.

Although integrin signaling has been found to be involved in multiple developmental stages of AS, there are still a wide range of pathological processes that need to be further explored. Future studies should focus on more selective integrin inhibitors and explore better ways to target integrin inhibitors to specific cell types to establish the worth of integrins as therapeutic targets for reducing AS and its complications.

Thrombosis. Thrombosis can occur in the arterial or venous circulation and has become a major health issue associated with high morbidity and mortality⁴⁰⁰. Arterial thrombosis caused by rupture of atherosclerotic plaque has been mentioned above.

$\alpha IIb \beta 3$ is the most abundant integrin in blood platelets⁴⁰¹ and is critical for arterial thrombosis⁴⁰². It binds to fibrinogen by the HHLGGAKQAGV sequence in the C-terminus of the fibrinogen γ chain and RGD sequences in the α chain³⁹⁸. Inside-out signaling activates $\alpha IIb \beta 3$, which contributes to platelet adhesion and aggregation. Outside-in signaling mediates platelet spreading and amplifies platelet thrombi⁴⁰³⁻⁴⁰⁶. Therefore, $\alpha IIb \beta 3$ antagonists, which are designed to block the ligand binding function of $\alpha IIb \beta 3$, are able to treat thrombosis, such as three current FDA-approved antiplatelet agents (abciximab, eptifibatide and tirofiban). Numerous oral compounds (orbofiban, sibrafiban, xemilofiban, lefradafiban, and roxifiban) have undergone substantial research. Because

of adverse effects such as increasing cardiovascular events, oral active antagonists have not yet received approval²⁴.

Compared to α IIb β 3, α v β 3 is widely expressed in tissues in addition to platelets⁴⁰⁷. A growing number of studies have shown that integrin α v β 3 is essential for mediating the adhesion of monocytes, platelets and endothelial cells. One of the key regulators of pathological angiogenesis and endothelial function is generally α v β 3 integrin⁴⁰⁸⁻⁴¹⁰. In vivo, it is expressed at low levels on quiescent endothelial cells but is markedly increased during wound angiogenesis, inflammation, and tumor angiogenesis²⁷⁹. In vitro, α v β 3 mediates the adherence of platelets to osteopontin and vitronectin⁴¹¹. It is also involved in the regulation of endothelial cell function^{412,413}, platelet aggregation and thrombosis^{414,415}. Moreover, clinical studies suggest that genetic variants of integrin β 3 may be used to predict venous thromboembolism in colorectal cancer patients⁴¹⁶. Therefore, integrin α v β 3 is an emerging approach for the identification and treatment of thrombotic-related diseases. Further research is still required to determine its reliability and specific mechanism.

In addition to integrins expressed on platelets, α 9 β 1, which is highly expressed in neutrophils, is also involved in thrombosis via several mechanisms⁴¹⁷⁻⁴¹⁹. α 9 β 1 is upregulated during neutrophil activation and interacts with VCAM-1 and polymeric osteopontin to mediate neutrophil chemotactic activity and stabilize adhesion to endothelial cells, leading to an increased risk of thrombosis^{420,421}. Moreover, apoptosis of neutrophils is inhibited by α 9 β 1 through the PI3K and ERK signaling pathways⁴²². Integrin α 9 can also modulate arterial thrombosis by enhancing NETosis. Treatment with anti-integrin α 9 antibody in wild-type mice inhibits arterial thrombosis, thereby revealing a novel role for integrin α 9 in the modulation of arterial thrombosis⁴²³. Due to the importance of both neutrophils and neutrophil extracellular traps for deep vein thrombosis and chronic thrombosis⁴²⁴⁻⁴²⁶, it may be a promising line of research to explore the role of α 9 β 1 in venous thrombosis.

Cardiac hypertrophy. Cardiac hypertrophy is defined as an increase in the size of cardiomyocytes. It is initially an adaptive response to physiological and pathological stimuli, but pathological hypertrophy usually progresses to heart failure⁴²⁷. Hypertrophy is directly related to β 1 integrin, including β 1A and β 1D^{428,429}. Deficiency of integrin β 1 induces hypertrophic changes with reduced basal contractility and relaxation⁴³⁰ and increases myocardial dysfunction after myocardial infarction⁴³¹. A previous study showed a correlation between the expression of integrin β 1 and angiotensin II type 1 (AT₁) receptor. An AT₁ blocker could promote the regression of cardiac hypertrophy by reducing integrin β 1 expression⁴³². Moreover, a β 3 integrin/ubiquitination (Ub)/NF- κ B pathway has been identified to contribute to compensatory hypertrophic growth⁴³³. FAK plays a key role in further proceeding the intracellular signals after integrin activation^{434,435}. Moreover, α 138, a muscle-specific integrin β 1-interacting protein, is important in protecting cardiac hypertrophy^{436,437}. ILK also emerges as a crucial player in mechanotransduction by integrins^{438,439}.

Cardiac hypertrophy is not autonomous and is entirely dependent on events occurring in muscle cells. Macrophages can also potentially contribute to the pathogenesis of cardiac hypertrophy. Integrin β 2 contributes to the adhesion of macrophages to endothelial cells, and β 2 blockade attenuates cardiac hypertrophy in mice⁴⁴⁰. The mechanism of integrins in cardiac hypertrophy needs to be further understood and explored, such as differences in signaling pathways that initiate compensatory and decompensated cardiac hypertrophy. Targeting integrins and signaling pathways may be novel strategies to control cardiac hypertrophy and prevent heart failure.

Integrins play vital roles in myocardial fibrosis. The expression and function of integrins are altered in the diseased heart⁴⁴¹. Targeting integrins and their associated proteins can be a potential

therapeutic target for myocardial fibrosis. Scar tissue size following heart injury is an independent predictor of cardiovascular outcomes⁴⁴². The differential expression of integrins $\alpha v\beta 3$ and $\alpha v\beta 5$ in cardiac fibroblasts of collagen V-deficient mice drives myofibroblast differentiation, and a specific inhibitor, cilengitide, can rescue the phenotype of increased postinjury scarring⁴⁴³. Integrins are also involved in aneurysms. The expression of both $\alpha 5$ and αv subunits in VSMCs plays an important role in assembling ECM within the vessel wall, and the loss of these two integrins leads to the formation of large aneurysms within the brachiocephalic/carotid arteries⁴⁴⁴. Thoracic aortic dissection (TAD) is also associated with integrins. Macrophage-derived legumain binds to integrin $\alpha v\beta 3$ in VSMCs and blocks it, thus attenuating Rho GTPase activation, downregulating VSMC differentiation markers and ultimately exacerbating the development of TAD⁴⁴⁵.

Integrin roles in infectious diseases

SARS-CoV-2 infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a dimeric virus in the *Betacoronavirus* genus⁴⁴⁶. The viral genome consists of four structural proteins, namely, spike (S), envelope (E), membrane (M), and nucleocapsid (N). The envelope, membrane and nucleocapsid are integrated into the viral envelope. A growing number of studies have focused on the integrin-mediated regulation involved in virus entry and spread (Table 1). $\alpha v\beta 6$ integrin has been reported to be of interest in inhibiting SARS-CoV-2 entry and treating coronavirus disease 2019 (COVID-19)-related diseases⁴⁴⁷. SARS-CoV-2 acts on human cells through angiotensin converting enzyme II (ACE2), and recent studies suggested that integrins might be the cell receptors for SARS-CoV-2⁴⁴⁸. The association between the S protein of SARS-CoV-2 and the ACE2 receptor has been established, but the S1 subunit contains a solvent-exposed RGD binding motif. It is recognized by integrins, particularly $\alpha 5\beta 1$ and $\alpha v\beta 3$ ^{449,450}. Moreover, the SARS-CoV-2 S protein was reported to interact with integrins independent of the RGD sequence, which helps to explain how SARS-CoV-2 and other viruses evolved to interact with integrins⁴⁵¹. Viruses bind cell-surface integrins via RGD. *In vitro* studies have provided evidence of cognate binding interactions between SARS-CoV-2 S proteins, integrin $\beta 1$ ^{452,453} and integrin $\beta 3$ ^{454,455}. Some drugs or methods that target integrins have been shown to have effects on infection. One study suggested that the ATN-161 molecule inhibited the S protein interaction with $\alpha 5\beta 1$ integrin, and the interaction of $\alpha 5\beta 1$ integrin and ACE2 represents a promising approach to treat COVID-19⁴⁵³. Mn^{2+} accelerates the cell entry of SARS-CoV-2 by inducing integrin extension and binding to high-affinity ligands⁴⁵⁶. In addition, integrins found on the surfaces of pneumocytes, endothelial cells and platelets may be vulnerable to SARS-CoV-2 virion binding. Below, we summarize six known integrins and their potential roles in SARS-CoV-2.

Although several approaches to integrin delivery to SARS-CoV-2 host cells have been discussed in the current literature, data from peer-reviewed experiments on this topic are still scarce. More data on integrin involvement and integrin ligands in SARS-CoV-2 infection, disease progression, and recovery are needed before clinically relevant imaging or therapeutic approaches can be realized.

Human immunodeficiency virus (HIV). Monocytes/macrophages play an important role in HIV transmission in all stages of HIV infection and disease. Adhesion molecules, including integrins, are recognized as the main factors that influence HIV viral replication. Previous studies proved that blocking αv and integrin binding triggered a signal transduction pathway, which inhibited the transcription of NF- κ B-dependent HIV-1⁴⁵⁷. Inhibition of β integrins (specific monoclonal antibody, small RGD mimetic compounds and RNA interference) proved that integrin $\beta 5$ mainly contributed

to the blockade of HIV-1 replication⁴⁵⁸. Other integrins, such as $\alpha\text{v}\beta 3$ and $\alpha 4\beta 7$, have also been proven to be associated with HIV. For example, the transactivating factor of HIV-1 binds to integrin $\alpha\text{v}\beta 3$, prompting neovascularization⁴⁵⁹. $\alpha 4\beta 7$, as a structurally dynamic receptor, mediates outside-in signaling to cells. The HIV envelope protein GP120 binds to and signals by $\alpha 4\beta 7$ ⁴⁶⁰; thus, targeting $\alpha 4\beta 7$ might be a new therapeutic method to prevent and treat HIV infection⁴⁶¹.

Other infectious diseases, such as the West Nile virus, enter cell entry by using the integrins $\alpha\text{v}\beta 1$ and $\alpha\text{v}\beta 3$ ^{462,463}. Ebola is related to integrin $\alpha 5\beta 1$, and herpes simplex virus type 1 (HSV-1) interacts with $\alpha\text{v}\beta 3$ ^{464,465}. Moreover, in immunized mice, the increased frequency of circulating integrin $\alpha 4\beta 7^+$ cells is correlated with protection against *Helicobacter pylori* infection⁴⁶⁶. $\beta 2$ integrin is important in the recruitment of dendritic cells to the infection site and may affect the initiation of innate immunity⁴⁶⁷. The overexpression and suppression of integrin $\alpha 6$ increases and decreases stemness phenotypes of HPV⁺ head-neck squamous cell carcinoma (HNSCC) cells, respectively⁴⁶⁸. Severe anti-programmed death-1 (PD1)-related meningoencephalomyelitis can be treated with anti-integrin $\alpha 4$ therapy⁴⁶⁹. Studies of murine and human cells expressing RGD-binding integrins proved that $\alpha\text{v}\beta 6$ and $\alpha\text{v}\beta 8$ heterodimers were involved in M1 and M3 infections⁴⁷⁰. These targets are of great significance for the mechanistic exploration and treatment of HIT and other infectious diseases, and more research data are needed in the future.

Integrin roles in autoimmune diseases

Integrins participate in the immune response against autoimmune diseases such as inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, which induces strong adhesion between lymphocytes, endothelial cells and epithelial cells by binding to ECMs and specific receptors. Many integrins are expressed in T cells, B cells, neutrophils, natural killer (NK) cells, monocytes, dendritic cells, macrophages and platelets⁴⁷¹.

Inflammatory bowel disease (IBD). IBD comprises a series of chronic recurrent intestinal diseases, including ulcerative colitis (UC) and Crohn's disease (CD)⁴⁷². The pathogenesis of IBD has not yet been clearly elucidated, and genetic predisposition, dysregulation of gut microbiota, or environmental factors cause an inappropriate and persistent immune response triggering impaired intestinal barrier function and stenosis⁴⁷³⁻⁴⁷⁶. Evidence suggests that IBD and its associated complications are not only modulated by sustained inflammation but also maintained by inflammation-independent mechanisms⁴⁷⁷. Integrins have been considered to be involved in both inflammatory and inflammation-independent mechanisms due to their important roles in immune cell recruitment and cell-ECM interactions in intestinal diseases^{478,479}.

Integrins $\alpha 4\beta 7$, $\alpha 4\beta 1$ and $\alpha \text{E}\beta 7$ are mainly involved in mediating lymphocyte homing to the intestinal mucosa. Integrin $\alpha 4\beta 7$ is specifically expressed on lymphocytes in the gastrointestinal tract and mediates the motility and adhesion of lymphocytes when inactive and activated, respectively^{480,481 482,483}. Integrin $\alpha 4\beta 7$ highly expressed on CD4⁺ memory T cells interacts with MAdCAM-1 expressed in intestinal inflammatory foci and regulates the homing of activated T cells during inflammation⁴⁸⁴⁻⁴⁸⁶. In addition, $\alpha 4\beta 7$ expression promotes the infiltration of regulatory T cells into the gut, whereas blockade reduces enteric homing of regulatory and effector T cells⁴⁸⁰. $\alpha 4\beta 1$ integrins (found on most leukocytes) are highly expressed in lymphoid tissues of the gut and interact with VCAM-1 expressed on the endothelium⁴⁸⁷⁻⁴⁸⁹. Adoptive transfer of $\alpha 4$ null T cells inducing defective homing of T cells to the inflamed tissues in immunodeficient mice significantly alleviated chronic colitis⁴⁹⁰. Blocking $\alpha 4$ -integrin prevents immune infiltration of the activated T-cell populations driving IBD^{488,491}. Integrin $\alpha \text{E}\beta 7$ is mainly expressed on the surface of CD8⁺ T

cells, Treg cells, CD69⁺αE⁺ intestinal tissue-resident memory T (TRM) cells, TH9 cells, and mucosal DC subsets, allowing them to adhere to the layer of the intestinal epithelium as a result of interacting with its ligand E-cadherin⁴⁹²⁻⁴⁹⁸. CD8⁺ T cells remain within the intestinal epithelium by downregulating α4β7 and upregulating αEβ7 to bind E-cadherin^{499,500}. Proinflammatory CD4⁺ T cells displaying Th17 and Th1 inflammatory phenotypes highly express αEβ7 in the colon and reduce the expression of associated genes, including inducible costimulator (ICOS), cytotoxic T-lymphocyte antigen (CTL-4), interleukin-10 (IL-10), and forkhead box protein P3 (FOXP3)⁴⁸⁹. A subset of CD4⁺ T cells with the natural killer group 2D (NKG2D) receptor also express integrin αEβ7, which is characterized by inflammatory and cytotoxic effects⁵⁰¹. Th9 CD4⁺ and CD8⁺ cells expressed increased αEβ7 compared with α4β7 expressed by Th17 and Th2 T cells⁴⁹⁶. In the colon of UC patients, the ability of αE⁺ dendritic cells (DCs) to generate regulatory T cells is attenuated and induces a Th1/Th2/Th17 phenotype in CD4⁺ effector T cells⁵⁰². The frequency and tolerogenic functionality of αE⁺ DCs are altered in the inflamed intestinal mucosa⁵⁰³. In addition to being physically retained in the intestinal epithelium, T lymphocytes expressing αEβ7 have direct cytotoxic activity against epithelial cells^{489,504}, and αE expression on a subset of resident memory CD4⁺CD69⁺ T cells accumulated in the mucosa of IBD patients predicts the development of flares⁴⁹⁵. Blockade of β7 integrin inhibits lymphocyte migration to gut-associated lymphoid tissue (GALT) and persistently suppresses adaptive immune-mediated IBD⁵⁰⁵⁻⁵⁰⁷. Additionally, integrin αvβ5 is highly expressed on mature intestinal macrophages but not other immune cells in the mouse intestine, acts as a receptor for apoptotic cell uptake and promotes tissue repair by regulating the homeostatic properties of intestinal macrophages, such as angiogenesis and ECM remodelling⁶⁴. Integrin αvβ6 is expressed only in epithelial cells and is mainly regulated by the integrin β6 (ITGB6) gene, which can increase integrin ligand expression, macrophage infiltration, proinflammatory cytokine secretion, and signal transducer and activator of transcription 1 (STAT1) signaling pathway activation. ITGB6 transgenic mice were found to have increased susceptibility to both acute and chronic dextran sulfate sodium-induced colitis, and αvβ6 induces intestinal fibrosis through the FAK/AKT pathway^{508,509}.

Anti-inflammatory treatment is ineffective in the development of fibrosis in IBD, a consequence of chronic inflammation. The mechanism of fibrosis is thought to be a continuous interaction between the stiffened ECM matrix resulting from the aberrant release of ECM components and cellular compartments⁵¹⁰. During tissue injury, matrix deposition and turnover are highly disrupted, resulting in dysregulated matrix stiffness in the ECM^{511,512}. Increased matrix stiffness triggers colonic myofibroblast activation to produce a fibrogenic phenotype and autoproagate fibrosis⁵¹³. The expression of genes related to inflammatory and fibrogenic remodelling was significantly increased, suggesting the presence of both fibrosis and inflammation in CD strictures. Interstitial ECM is the most fundamental in the process of fibrosis, including the latent state of TGF-β, EGF, fibroblast growth factor (FGF) and other molecular fibrotic mediators⁵¹⁴. αv and β5 are the major integrin isoforms in intestinal fibrosis, and their main function is to activate TGF-β. αvβ8 binds to a linear RGD motif of latent TGF-β, which subsequently recruits MMP14 and then releases TGF-β through proteolytic cleavage. αvβ8 can also activate TGF-β independently from cytoskeletal forces without release from latent peptide²⁵⁶. *In vivo* studies have shown that overexpression of αvβ6 in the epidermis activates TGF-β1, resulting in chronic ulcers and fibrosis⁵¹⁵. Latent TGF-β1 was also activated through integrin αvβ3 expressed in human and rat intestinal smooth muscles⁵¹⁶, leading to the production of collagen I and fibrosis in CD⁵¹⁷. The

elevated expression of $\alpha 3 \beta 1$ can enhance the expression level of MMP9 in keratinocytes through the TGF- β pathway⁵¹⁸.

Natalizumab (anti- $\alpha 4$ antibody) and vedolizumab (anti- $\alpha 4 \beta 7$ antibody) have been approved for maintaining clinical remission in patients with IBD^{519,520}. Natalizumab was the first drug approved for the treatment of Crohn's disease, but its use has been limited because of its risk of progressive multifocal leukoencephalopathy^{521,522}. Compared with natalizumab, vedolizumab acts specifically on $\alpha 4 \beta 7$ to selectively inhibit the trafficking of lymphocytes in the intestine. It has been approved for the treatment of IBD with few systemic adverse effects^{523,524}. Currently, several anti-integrin drugs are undergoing more clinical trials. Abruimab, a fully human monoclonal IgG2 antibody against the $\alpha 4 \beta 7$ integrin heterodimer, shows encouraging results in two phase II studies on moderate to severe CD and UC (CD: NCT01696396, UC: NCT01694485)^{525,526}, while no phase III clinical trial registration information has been found to date. Etrolizumab is a monoclonal antibody that specifically targets the $\beta 7$ subunit of $\alpha 4 \beta 7$ and $\alpha E \beta 7$ integrins to block their interaction with MAdCAM-1 and E-cadherin, respectively, which is in an ongoing robust phase II study on UC and a phase III study on CD. Notably, a phase I study of etrolizumab to evaluate its pharmacokinetics, pharmacodynamics and safety in pediatric patients 4 to <18 years of age with moderate to severe ulcerative colitis (UC) or with moderate to severe CD has been registered. AJM300, an oral $\alpha 4$ integrin antagonist characterized by mild adverse effects sharing a similar mechanism with natalizumab^{527,528}, is currently in a phase III study of patients with active UC (NCT03531892).

Multiple sclerosis (MS). MS is an autoimmune disease driven by agnogenic chronic inflammation in the central nervous system (CNS). It is characterized by inflammation in the brain and spinal cord that causes the demyelination of neurons, which blocks nerve signal transmission⁵²⁹. MS patients show sensory disorders, motor dysfunction, optic neuritis, and other physical and cognitive disorders⁵²⁹. Currently, there are approximately 2.5 million people with MS worldwide⁵³⁰, which is a huge burden to society. The infiltration of autoreactive immune cells from peripheral circulation into the brain is the core pathogenesis of MS⁵³¹. Preventing the infiltration processes of leukocytes into the CNS is an effective way to curb the progression of MS. Therefore, the adhesion molecules involved in leukocyte activation and mediating leukocyte migration to the CNS have received extensive attention. Among them, leukocyte integrins, as mentioned above, play important roles in regulating leukocyte function. In fact, in recent years, studies on the role of integrins in MS have yielded exciting results. In particular, integrin $\alpha 4$. Integrin $\alpha 4$ pairs with integrin $\beta 1$, $\beta 2$, or $\beta 7$, of which integrin $\alpha 4 \beta 1$ is regarded as an important therapeutic target for MS. Integrin $\alpha 4 \beta 1$ is also called very late antigen-4 (VLA-4), which binds primarily to VCAM-1 and ECM ligand fibronectin deposited in inflamed tissues. The interaction between integrin $\alpha 4 \beta 1$ and VCAM-1 promotes the homing of leukocytes into the CNS, which accelerates the progression of MS. Disturbing the interaction between integrin $\alpha 4 \beta 1$ and VCAM-1 has been shown to effectively retard the progression of MS. As early as 1992, Yednok et al. demonstrated that inhibiting integrin $\alpha 4 \beta 1$ could effectively suppress the accumulation of leukocytes in the CNS, and they recommended anti-integrin $\alpha 4 \beta 1$ antibody as therapeutic for MS⁵³². Natalizumab, a humanized IgG4 antibody that recognizes integrin $\alpha 4$, has been confirmed to significantly reduce the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing MS. It could also enhance the therapeutic effect of interferon- β 1 α (IFN- β 1 α) on MS when combined with it. However, it has been reported that long-term use of natalizumab may cause serious infection

complications, such as progressive multiple leukoencephalitis (PML). Therefore, there is still a long way to go for the treatment of MS by targeting integrin $\alpha 4 \beta 1$. Novel integrin $\alpha 4 \beta 1$ inhibitors may be the key to overcoming MS in the future.

Rheumatoid arthritis (RA). RA is a chronic and systemic autoimmune inflammatory disease that is characterized by synovial hyperplasia, articular inflammation and synovial invasion into adjacent cartilage⁵³³. Integrins play an important role in the pathophysiology of RA, such as promoting communication between ECM proteins and rheumatoid cells and facilitating angiogenesis. $\alpha \nu \beta 3$ and $\alpha 5 \beta 1$ are expressed on synoviocytes, including chondrocytes, fibroblasts and endothelial cells, and synovial-infiltrated cells, including T cells, neutrophils, B cells and macrophages, which promote binding to cartilage-pannus junctions and fibroblast invasion⁵³⁴⁻⁵³⁶. Fibronectin upregulated in inflamed articular tissues is a ligand of $\alpha \nu \beta 3$ and $\alpha 5 \beta 1$ ⁵³⁴. $\alpha 5 \beta 1$ promotes the proliferation of naive T cells and memory T cells by binding to fibronectin⁵³⁴. In RA, osteoclasts express $\alpha \nu \beta 3$ at high levels, and $\alpha \nu \beta 3$ promotes bone resorption because of osteoclast migration by recruiting c-Src kinase⁵³⁷. Macrophages and Th cells expressing $\alpha \nu \beta 3$ and $\alpha 5 \beta 1$ produce IL-17, IL-1 and tumor necrosis factor (TNF)- α , which lead to the activation of synovial fibroblasts^{538,539}. Neutrophils express $\alpha \nu \beta 3$ and $\alpha 5 \beta 1$, which contribute to neutrophil migration and mediate cell adhesion to neutrophil extracellular traps (NETs)⁵³⁶. $\alpha \nu \beta 3$ expressed by Th17 cells enables them to adhere to osteopontin, which serves as a costimulator of IL-17⁵⁴⁰. Inhibition of $\alpha \nu \beta 3$ prevents osteoclast-mediated bone destruction by reducing Th17 activation and receptor activator of nuclear factor-kappa B ligand (RANKL) levels⁵⁴⁰. In addition, integrins in RA could promote new vascularization, accumulation of synovial cells, and the secretions lead to hypoxia-inducible factor 1 (HIF-1) release, which acts as a stimulator of VEGF, PDGF and fibroblast growth factor 2 (FGF-2). These growth factors induced overexpression of $\alpha \nu \beta 3$ and $\alpha 5 \beta 1$ in smooth muscle cells, endothelial cells and platelets. Upregulated $\alpha \nu \beta 3$ and $\alpha 5 \beta 1$, in turn, further activate proinflammatory cytokine production, which mediates smooth muscle cell and endothelial cell proliferation and migration and platelet activation⁵⁴¹⁻⁵⁴³. Furthermore, $\alpha 9$ is reported to be overexpressed both in animal models of arthritis and in RA patients, and increased $\alpha 9$ expression precedes the onset of arthritic symptoms. Blocking $\alpha 9$ inhibits fibroblast-like synoviocyte (FLS) activation against arthritis through a nonimmune-mediated mechanism⁵⁴⁴.

In addition to the abovementioned diseases, integrins and their ligands are also involved in the progression of other autoimmune diseases. Multiple sclerosis is a demyelinating and inflammatory disorder of the CNS. Integrins such as $\alpha 4 \beta 7$, $\alpha E \beta 7$, and $\alpha 4 \beta 1$ and their ligands are involved in the progression of multiple sclerosis by modulating the processes of immune cells⁵⁴⁵. B cells, neutrophils, and macrophages express high amounts of $\alpha M \beta 2$, and systemic lupus erythematosus (SLE)-IgG enhances $\alpha M \beta 2$ -mediated adhesion to fibrinogen in systemic lupus erythematosus⁵⁴⁶. Inhibition of the $\alpha 1 \beta 1$ interaction with collagen leads to reduced accumulation of epidermal T cells, and the presence of anti- $\alpha 6$ -integrin autoantibodies due to altered laminin integrity has been observed in psoriasis^{547,548}.

Integrin roles in other diseases

In addition to the above reports of integrin-related diseases, integrins also contribute to eye development and pathological processes, including the healing process of keratoconus injuries, allergic eye disease, cornea, lens opacification, diabetic retinopathy, glaucoma, eye infection, axon degeneration in the optic nerve and scleral remodelling in high myopia⁵⁴⁹. For example, $\alpha 5 \beta 1$ integrin participates in anchoring or integrating transplanted stem cells to the trabecular meshwork

in the eye for regeneration, and this might be a way for stem cell-based therapy for glaucoma⁵⁵⁰. Vitronectin/ α v integrin-mediated NF- κ B activation has been proven to induce inflammatory gene expression in bone marrow-derived macrophages. This will be an important step in the inflammatory process of dry eye disease (DED)⁵⁵¹. In addition, drug discovery focused on integrin α β 2, providing a marketed small molecule, LifiteGrast, for the topical treatment of DED⁵⁵². For ophthalmic diseases, integrin inhibitors were proven to be effective in several preclinical models and have reported promising results in clinical trials⁵⁵³.

Integrins are also promising antiresorptive therapeutic targets⁵⁵⁴. Osteoactivin promotes integrin β 1 expression and leads to ERK activation. The expression of several genes upstream of osteoactivin was blocked, and the mRNA and protein levels of osteoactivin were decreased by dexamethasone. This ultimately inhibits integrin β 1-ERK activation, resulting in reduced osteogenesis⁵⁵⁵. In addition, α v β 3 integrin participates in osteoclast differentiation and resorption, and α v β 3 integrin antagonists are considered to be effective drugs for postmenopausal osteoporosis⁵⁵⁶. L-000845704, as an α v β 3 integrin antagonist, was reported to inhibit bone resorption and improve bone mass in women with postmenopausal osteoporosis. A phase II clinical trial of 227 postmenopausal women with osteoporosis showed that L-000845704 could decrease the bone absorption marker carboxyterminal telopeptides of type I collagen (CTX) and increase the bone mineral density of the lumbar spine and femoral neck⁵⁵⁷.

Alzheimer's disease (AD), characterized by cognitive decline, is a neurodegenerative disorder and is associated with amyloid- β (A β) plaque deposition, neuronal loss, and hyperphosphorylation of tau protein. Astroglia-associated AD is known to be caused by the interaction of amyloid β oligomers with β 1-integrin. This enhanced β 1-integrin and NADPH oxidase (NOX) 2 activity by NOX-dependent mechanisms⁵⁵⁸. In transgenic AD models, neutrophil depletion or inhibition of neutrophil trafficking by lymphocyte function-associated antigen (LFA)-1 blockade can reduce AD-like neuropathology and improve memory in mice showing cognitive dysfunction⁵⁵⁹. The counterligand of VCAM-1- α 4 β 1 integrin, expressed by a large proportion of blood CD8⁺ T cells and neutrophils, was abundant on circulating CD4⁺ T cells in AD mice⁵⁶⁰. This suggested that α 4 integrin-dependent leukocyte trafficking promoted cognitive impairment and AD neuropathology. Thus, the blockade of α 4 integrins might be a new therapeutic method for AD. Recently, compared to isotype control injections without changing amyloid- β plaque load in a mouse model of AD, an antibody recognizing α 4-integrin therapy reduced astroglia, microglia, and synaptic changes in APP/PS1 mice⁵⁶¹.

CHALLENGES AND OPPORTUNITIES: INTEGRIN-TARGETING DRUG DISCOVERY FROM BENCH TO CLINICAL

Integrins have historically been promising and challenging targets for the treatment of multiple diseases. The targeting integrin-related indications are summarized in Table 2, referring to cancer, fibrotic diseases, cardiovascular disease, viral infections, autoimmune diseases, and so on. The ongoing clinical studies of integrin-targeting drugs intended as disease therapies are summarized in Table 3 (from 2019 to 2022). Currently, there are approximately 90 kinds of integrin-targeting therapies in clinical trials, including integrin antagonists and imaging agents (search at <https://www.clinicaltrials.gov>, <https://www.clinicaltrials-register.eu>, <https://www.australianclinicaltrials.gov.au>, <http://www.chictr.org.cn> using the search term “integrin”) (Table 4). Among them, approximately two-thirds of drugs or imaging agents are being studied in Phase I to Phase III, and nearly one-third of integrin-targeting therapies are terminated, withdrawn or no progression. The

related reasons are manifold, including delayed and difficult enrollment, lack of efficacy, safety concerns, commercial decision making and lack of funding. In 2022, the positive results in clinical trials show the new dawn of integrin-targeting therapies. For example, carotegrast (AJM300) is an oral, targeting $\alpha 4$ -integrin small molecule antagonist, and the phase III study results showed that carotegrast was well tolerated and induced a clinical response in patients with moderately active ulcerative colitis who had an inadequate response or intolerance to mesalazine. Carotegrast, as the first oral anti-integrin drug, was approved by Japan's PMDA on March 28, 2022, for moderate ulcerative colitis (only when 5-aminosalicylic acid preparations are not adequately treated) ⁵⁶². Pliant Therapeutics, Inc. (PLRX) reported positive results for PLN-74809, the oral dual $\alpha v\beta 1/\alpha v\beta 6$ inhibitor, in the INTEGRIS-IPF Phase IIa study, which met its primary and secondary endpoints, demonstrating that PLN-74809 was well tolerated over the 12-week treatment period and showed a favorable pharmacokinetic profile. Herein, we summarize the main progression of small molecules, synthetic mimic peptides, antibodies, ADCs, peptide drug conjugates (PDCs), nanotherapeutic agents, CAR T-cell therapy, and imaging agents.

Small-molecule compounds and peptides

Small-molecule drugs accounted for the largest part of the ongoing clinical trials given their cost advantage, safety perspective, pharmacokinetic profiles, administration route, etc., compared with antibodies or larger conjugate molecules. Historically, many RGD-binding integrin drug discovery initiatives have been carried out to target the orthosteric binding sites, but most of these drug discoveries have not been successful due to the potential binding-induced conformational shifts of integrin from a low-affinity to a high-affinity state ²⁸. These reactions have been found for $\alpha IIb\beta 3$ RGD mimetics such as eptifibatide and $\alpha v\beta 3$ integrin RGD mimetics cilengitide, which shows direct agonist and proangiogenic effects at low doses.

In light of this potential effect, some research groups switched to identify non-RGD or pure small-molecule integrin antagonists and inhibitors binding allosterically. Another problem for drug discovery based on RGD-integrins is the undesirable physicochemical properties due to zwitterionic or amphoteric design. Therefore, novel chemotypes that are nonzwitterionic would be beneficial for oral bioavailability ²⁸. One of the first breakthroughs of non-RGD mimetics is RUC-1 and its more potent derivatives RUC-2 and RUC-4, targeting $\alpha IIb\beta 3$ outside-in signaling pathways, which do not induce integrin activation ^{563,564}. A phase I, dose-escalation study showed that RUC-4 administered subcutaneously provided rapid, high-grade inhibition of platelet aggregation and that it is also safe and well tolerated and has the potential to be used at the point of first contact before primary coronary intervention ⁵⁶⁵. RUC-4 was designed as a nonzwitterionic chemotype that does not potentially induce conformational shifts, which provides a promising approach for the discovery of αv -containing integrin antagonists. Other $\alpha v\beta 3$ small-molecule pure antagonists, TDI-4161 and TDI-3761, have been designed and proven to not induce the conformational change tested by cryogenic electron microscopy imaging of integrin conformations ⁵⁶⁶. Recent studies have shown that failed integrin small-molecule inhibitors in clinical trials are capable of stabilizing the extended open conformation with high affinity ⁴⁹. Closing inhibitors show a simple chemical feature with a polar nitrogen atom that stabilizes integrins in their bent-closed conformation by intervening between the serine residue and MIDAS ⁴⁹.

The rational design of molecules that bind to integrin outside the ligand binding site, the allosteric site, could prevent integrin activation by sealing the orthosteric site or by keeping or promoting the conformation at a low-affinity state ²⁸. There are only reported some antibodies

targeting the allosteric site, such as natalizumab⁵⁶⁷. In recent years, novel chemotypes with high-quality orally bioavailable inhibitors have made large breakthroughs, such as carotegrast⁵⁶², PLN-74809⁵⁶⁸, and PTG-100⁵⁶⁹. Although PTG-100, an oral $\alpha 4\beta 7$ antagonist peptide, initially did not meet the primary endpoint in a phase IIa study, it showed proof-of-concept efficacy in patients with moderate-to-severe active UC, and the related data also suggested that local gut activity of an oral $\alpha 4\beta 7$ inhibitor is important for efficacy for UC treatment, which is different from full-target engagement in blood. Other orally bioavailable inhibitors under ongoing clinical studies include IDL-2965 and MORF-057, developed by EA Pharma, Pliant, Protagonist, Indalo, and Morp hic, respectively (Supplement Table S2).

Antibodies, ADCs and PDCs

Many monoclonal antibodies (mAbs) targeting integrins are now available as research tools or life-changing therapeutics and are classified into three groups: inhibitory mAbs acting as antagonists, stimulatory or activation-specific mAbs, and nonfunctional mAbs⁵⁷⁰. Anti-integrin mAbs are essentially competitive inhibitors, and most act as allosteric inhibitors, recognizing various parts of the ectodomain of subunit- or conformation-specific integrins⁵. Abciximab, an antibody against integrin $\alpha IIb\beta 3$, has undergone extensive clinical studies (EPIC, EPILOG, CAPTURE)⁵⁷¹ and has been approved for use during PCI or in patients with unstable angina/non-ST-elevation myocardial infarction that did not respond to traditional treatment⁸⁴. The integrin $\alpha 4$ antibody natalizumab has shown considerable therapeutic effects on multiple sclerosis⁵⁶². Vedolizumab, an integrin $\alpha 4\beta 7$ antibody, was used to treat Crohn's disease and ulcerative colitis⁵⁶². Recently, abrilumab (Amgn), also called AMG-181, targeting the integrin $\alpha 4\beta 7$ heterodimer, showed encouraging results in a phase II study on moderate to severe CD and UC⁵⁶². AJM300 is an oral antagonist of integrin $\alpha 4$, which is currently in a phase III study of patients with active UC⁵⁶². Integrin av mAbs have a range of selectivity profiles, which are beneficial in the validation of integrin targets in disease, but highly selective av small-molecule inhibitors are unavailable⁵⁷². Currently, an example is P5H9 (MAB2528) for $\alpha v\beta 5$ ⁵⁷³. Currently, the antibody in the highest clinical trial stage is Etrolizumab, targeting integrin $\beta 7$, which recently carried out a head-to-head comparison, phase III study, with infliximab, approved anti-TNF- α antibody, for the treatment of moderately to severely active ulcerative colitis (GAEDENIA)⁵⁷⁴. Overall, the GARDENIA study demonstrated that etrolizumab and infliximab achieved the same efficacy and safety endpoints at weeks 10 and 54⁵⁷⁵. This head-to-head comparison also shows that the safety of the two in long-term results at one year is comparable.

Integrins, as cell surface receptors, are overexpressed in specific diseased tissues, which makes them design ADCs and PDCs to conjugate integrin binding antibodies and peptides to bioactive moieties. Indeed, recent clinical trials (NCT04389632) and (CTR20221496) have been initiated to investigate an ADC and PDC that selectively recognize $\beta 6$ and $\alpha v\beta 3$, respectively, to target solid tumors.

Nanotherapeutic agents

Integrins have been considered potential targets for cancer treatment for a long time, but there are no approved anticancer drugs targeting integrin. Nanotherapeutics approaches applied in targeting integrin therapies probably overcome the limitations of conventional therapies used in cancer treatment to achieve more precise, safer, and highly effective therapeutics. Integrins, overexpressed on the surface of cancer cells, are viewed as beneficial targets for the preferential delivery of genes or drugs into cancer cells⁵⁷⁶. The delivery of RGD-based peptides to integrin

receptors could be helpful for the binding and liberation of drugs in the tumor vasculature. The majority of nanoparticles (NPs) modified with RGD peptide and loaded with nucleotides or drugs have been developed in preclinical studies. For example, $\alpha\beta3$ integrin-targeting NPs obtained by coupling RGD ligands to the surface of PEGylated chitosan-poly(ethylene imine) hybrids showed high gene silencing efficiency and facilitated efficient siRNA delivery⁵⁷⁷. The RGD motif was also used to connect to PEG-PLA and loaded with paclitaxel (PTX) and its derivative docetaxel (DTX) to avoid their disadvantages of low solubility and dose-limiting toxicity⁵⁷⁸. The cyclopeptide isoDGR is found in aged fibronectin, where it is formed by deamidation of Asn in an asparagine-glycine-arginine (NGR) site, which is a new $\alpha\beta3$ -binding motif with high affinity and does not induce integrin allostery and activation^{579,580}. Therefore, in future studies, isoDGR-based nanotherapeutic agents have potential applications in cancer treatment.

CAR T-cell therapy

Integrins are also used in immunotherapy by conjugating to CAR T cells. Currently, there are two kinds of CAR T-cell therapies in clinical studies. OPC-415 targeting $\beta7$ and Marnetegrane autotemcel targeting $\beta3$ were developed by Otsuka and Pocket, respectively. The active conformer of integrin $\beta7$ served as a novel multiple myeloma (MM)-specific target, and MMG49, in the N-terminal region of the $\beta7$ chain, derived CAR showed good anti-MM effects without normal hematopoietic cell damage²⁷. Currently, OPC-415 targeting $\beta7$ CAR T-cell therapy is in a phase II study. Integrin $\alpha\beta3$ - and $\alpha\beta6$ -CAR T cells also show therapeutic potential in solid tumors, such as melanoma, triple-negative breast cancer, and cholangiocarcinoma^{581,582}.

Imaging agent

Molecular imaging is an important part of precision medicine and plays an important role in the early diagnosis, staging, prognostic evaluation, individualized treatment and efficacy monitoring of major diseases such as cancers. 2-Deoxy-2-[¹⁸F]fluoro-d-glucose ([¹⁸F]FDG) positron emission tomography combined with low-dose computed tomography ([¹⁸F]FDG-PET/CT) is currently the gold standard for the clinical imaging diagnosis of various malignant tumors. However, in recent years, the development of clinical application of PET imaging has entered a bottleneck period, mainly due to the complex preparation of positron-electron drugs and the high imaging cost. Compared with PET technology, single photon emission computed tomography (SPECT) has lower equipment and drug costs, a higher clinical penetration rate and a better application foundation. However, the lack of effective imaging agents, such as ¹⁸F-FDG, limits the SPECT technology to play a greater role in tumor diagnosis and efficacy evaluation. Currently, SPECT imaging agents in the clinical phase mainly focus on integrin $\alpha\beta3$ due to its overexpression on the surface of tumor neovascular endothelial cells and many tumor cells and the high affinity of polypeptides containing RGD sequences. Therefore, targeting $\alpha\beta3$ SPECT imaging agents has been developed. ^{99m}Tc-3PRGD2 is the first broad-spectrum SPECT tracer developed by Peking University targeting integrin $\alpha\beta3$ for detecting tumors, imaging angiogenesis, and evaluating tumor response to therapy⁵⁸³. The phase III study showed the good efficacy of ^{99m}Tc-3PRGD2 for the evaluation of lung cancer progression. $\alpha\beta6$ integrin also serves as a promising target for cancer imaging. ¹⁸F-FP-R₀1-MG-F₂ is an integrin $\alpha\beta6$ -specific PET imaging agent developed by Stanford University. The pilot-phase PET/CT study showed good safety and radiation dose performance in pancreatic cancer patients⁵⁸⁴. Except for pancreatic cancer, the potential indications include idiopathic pulmonary fibrosis (IPF), primary sclerosing cholangitis, and COVID-19 pneumonia.

CONCLUSIONS AND PERSPECTIVES

27 Decades of investigation into the biological functions of integrins have suggested that integrins exhibit roles in the regulation of many aspects of human health and disease, and their molecular mechanisms and signal transduction are also strikingly complex. Considering the width and feasibility of therapeutic options, targeting integrins is an important avenue to explore. In recent decades, targeting integrin drug discovery has continued to move forward with its twists and its turns. Many of the lessons learned from the past are also valuable to achieve a heavy bomb in this field. We give perspective from three aspects: 172 basic research, clinical research, and translational research.

37 For basic research, research on integrins is quite mature but also a newly reawakened field. It is important to validate the function of integrin targets in clinically predictive disease models and analyze the expression landscape in a large-scale cohort in different diseases and states, which contributes to success in clinical trials. Notably, current studies of integrin-targeted strategies are focused not only on extracellular but also on intracellular targets that involve both inside-out and 14 outside-in signaling pathways. Several adaptors are known to interact with the cytoplasmic tails of β -integrins, including $\text{G}\alpha 13$, focal adhesion kinase, ILK, and Syk, Src family kinases. For example, $\text{G}\alpha 13$ binds directly to the ExE motif in the cytoplasmic domain of the integrin β subunits, and this 181 binding occurs only during early outside-in signaling. A myristoylated ExE motif peptide selectively inhibits outside-in signaling, platelet spreading and the second wave of platelet aggregation by selectively inhibiting $\text{G}\alpha 13$ -integrin interaction. This strategy to inhibit outside-in signaling not affect primary platelet adhesion and aggregation, but limit the size of a thrombus to prevent vessel occlusion^{398,586}. 14-3-3 ζ synergizes c-Src to $\beta 3$ -integrin, and forms the 14-3-3 ζ -c-Src-integrin- $\beta 3$ complex during platelet activation. Interference with the formation of complex by myristoylated-KEATSTF-fragment (KF7) and 3',4',7'-trihydroxyisoflavone (THO) is a strategy to selectively 14 inhibit outside-in signaling without disrupting the ligand binding of integrins⁵⁸⁶. Targeting intracellular targets via outside-in signaling pathways may provide new sights for avoiding the formation of potentially undesired conformational states. Considering the substantial clinical failure in targeting integrin in the orthosteric binding sites due to activation of integrin signaling, identification of other allosteric sites is urgently needed to develop candidates that target integrin at other sites. Clearly, the conformational states shift exists in $\alpha \text{v}\beta 3$ and $\alpha \text{IIb}\beta 3$ induced by their inhibitors, but it is not clear to other 7 RGD-binding integrins or leukocyte cell adhesion integrins, collagen binding integrins, laminin binding integrins. Crystallographic structural analysis would be helpful to reveal the conformational change mechanism. Considering the width and complexity of biological function and signaling within the integrin family, whereas 5 only a small part of integrin biology is known, further research is required to explore the much unknown field.

For clinical research, targeting integrin therapeutics may have their greatest utility as combination therapies with other agents considering the potential function of integrin inhibition in overcoming acquired resistance to chemotherapy, radiotherapy, targeted therapy (including VEGFR inhibitors) or therapy targeting the immune microenvironment. Currently, due to the complexity of solid tumors, the combination therapy of anti-tumor drugs with different mechanisms or targets is the mainstream strategy in the clinic 152 to improve anti-tumor efficacy and overcome or delay drug resistance. The identification of robust biomarkers and imaging technology applications are required to find patients with tumors whose progression is driven by integrin signaling or to measure specific integrin expression levels in the recruited subjects, which could guide the best clinical use of integrin inhibitors. In addition to focusing on efficacy of integrin antagonists, we should also pay special

attention to the adverse effects of integrin antagonists in clinical applications or clinical trials. For example, the oral α Ib β 3 antagonists were associated with increased mortality compared to intravenous administration²⁴. One explanation could be that some of the drugs have agonist-like activity, which may trigger "outside-to-inside" signals within the receptor-cell membrane complex, affect receptor conformational status and competency, membrane fluidity, and calcium metabolism⁵⁸⁷, and potentially activate GPIIb/IIIa receptor, maintain procoagulant activity and P-selectin expression^{588,589}. Moreover, progressive multifocal leukoencephalopathy (PML), a rare but serious opportunistic infection of the central nervous system, is the most concerning adverse event of integrin antagonists. Currently approved α 4 integrin antagonist, natalizumab, is at high risk of developing PML⁵⁹⁰. Efalizumab, an α L β 2 integrin antagonist previously approved for the treatment of plaque psoriasis^{591,592}, was also withdrawn from the market due to the incidence of PML⁵⁹³. A restricted risk management plan is necessary to help reduce the potential risk of PML in clinical practice and clinical trials⁵⁹⁴. For example, patients with any neurologic symptoms, immunocompromised conditions, or those receive concurrent immunosuppressive therapy or anti-TNF α antibodies should be precluded^{527,594}. Therefore, these related adverse effects should be taken into consideration in ongoing clinical trials and systematic post-marketing surveillance will contribute to the success of translational research and drug discovery of targeting integrin therapeutics.

For translational research, developing small molecules with new chemotypes, high affinity and good pharmacokinetic profile for oral dosing is challenging but has a huge market. The identification of novel non-RGD or pure antagonist chemotypes via high-throughput screening and targeting integrin and ECM interactions are important drug discovery directions. In addition, given the multifaceted roles of integrins as signaling molecules, dual-target drug development and multi-indicative simultaneous development will improve the efficiency and success rate. Dual-target novel agents may overcome resistance compared with single-target drugs and often improve treatment outcomes and have more predictable pharmacokinetics profiles than combination therapies. The development of dual-target inhibitors has become an attractive research field for human cancer treatment and may provide synergistic anticancer effects. For example, integrins combined with other cell adhesion molecules, such as CD44 and dual-target inhibitors of tubulin and α v-integrin, for cancer treatment are an untapped research field. Currently, for cardiovascular diseases and ulcerative colitis treatment, anti-integrin therapeutics have been a major success. In the future, targeting integrin drug discovery is gradually going forward to unmet medical needs, such as IPF, NASH, aggressive or resistant malignancy, etc. Based on robust target validation, integrins will provide new significant opportunities for a variety of indications.

In summary, integrins play a crucial role in human health and disease due to their expression in multiple cell types and widespread involvement in cellular processes. Knowledge of integrins in various diseases is progressing, but the drug discovery process is less than satisfactory. We hope the progression in basic research, clinical research, and translational research will establish realizable access for developing effective drugs for unmet medical needs.

ACKNOWLEDGMENTS

This research was funded by National High Level Hospital Clinical Research Funding (Scientific and Technological Achievements Transformation Incubation Guidance Fund Project of Peking University First Hospital) (No.2022CX11, No. 2022RT01); National Key R&D Program of China (No. 2020YFC2008304); National Natural Science Foundation of China (No. 81973320 and No.

81903714). Thanks to Pharmacodia database for retrieving clinical trial data.

AUTHOR CONTRIBUTIONS

X.P. and Y.C. conceived and organized the manuscript. X.P., Q.X., X.H., Z.Q., H.Z., Z.L., and Y.G. wrote the manuscript, prepared the figures and contributed to the discussion. R.X. and N.Z. researched data and prepared table. All authors have read and approved the article.

ADDITIONAL INFORMATION

The authors declare no competing interests.

Figure Legends

Fig. 1. Timeline of the historical milestone for the study of integrin receptors and their main antagonists and agents in the past four decades.

Fig. 2. The primary structure and representative conformations of integrins. a. Organization of domains within the primary structures. b. Arrangement of domains within the representative 3D crystal structure of integrins. c. Conformational change of integrins: bent closed, extended closed, and extended open conformations.

Fig. 3. Classification, distribution, and ligands of integrins. The inner ring shows the 24 integrins that are composed of 17 α subunits and 8 β subunits. They are divided into four categories, namely, RGD-binding integrins, leukocyte cell adhesion integrins, collagen binding integrins, and laminin binding integrins, according to their distribution, ligand specificity, and functions. The middle ring shows the distribution of integrins in different cell types. The outer ring indicates the ligands bound by different types of integrins

Fig. 4. Schematic overview of integrin activation-associated signalling cascades. Integrin activation is regulated by multiple external signals, such as ECM, mechanotransduction or signaling from non-ECM ligands, including growth factor receptors, hormones, and small molecules, which is termed the “outside-in” mechanism. ECM or non-ECM ligand binding and force application results in integrin clustering and initiates downstream signaling to the actin cytoskeleton through recruited talin and vinculin, where actin can simultaneously pull on integrins and further in turn promote force generation. The “outside-in” mechanism then triggers various signaling cascades that ultimately result in cell survival, proliferation, cell spreading and even tumorigenesis and metastasis. On the plasma membrane, there is also an “inside-out” mechanism, which regulates the displacement of intracellular integrin inhibitors and allows talin or kindlin binding to integrin β - tails, controlling integrin affinity for ECM components. For example, in neutrophils, both Talin-1 and Kindlin-3 are rapidly recruited to activate $\beta 2$ integrins induced by extracellular chemokines binding to GPCR (G-protein coupled receptor). Solid arrows indicate activation, the dotted line indicates recruiting, and the solid blunt end arcs indicate inhibitory effects.

Fig. 5. The expression and function of major integrins and their related cancer types and metastatic sites. The expression of integrins can vary considerably between normal and tumor tissue and is also associated with cancer types and organotrophic metastasis.

Fig. 6. Roles of integrins in fibrosis processes in NASH, PH, and ADPKD. The lower part of the circle shows the role of integrins in liver fibrosis in NASH. In hepatic cells (HCs), activated integrin $\alpha 9 \beta 1$ is endocytosed by hepatocytes and secreted in the form of extracellular vesicles (EVs), which are further captured by MoMFs. Captured integrin $\alpha 9 \beta 1$ mediates MoMF adhesion to liver sinusoidal endothelial cells (LSECs) by binding to VCAM-1, which accelerates liver fibrosis. In HSCs, integrin $\alpha 8 \beta 1$ promotes liver fibrosis by activating TGF- β . The binding of integrin $\alpha v \beta 3$ with OPN could promote laminin and α -SMA expression, which causes ECM accumulation and fibrosis

progression. Integrin $\alpha\text{v}\beta 5$ also binds with OPN and enhances liver fibrosis, but the underlying mechanism still needs to be clarified. In CD4⁺ T cells, the adhesion between integrin $\alpha 4\beta 7$ and HC expressing MAdCAM-1 recruits CD4⁺ T cells to the liver, which induces liver inflammation and fibrosis. The left part of the circle shows the role of integrins in intimal fibrosis in PH. In the progression of PH, integrin $\alpha 1$, $\alpha 8$, αv , $\beta 1$, and $\beta 3$ are upregulated, and $\alpha 5$ is downregulated in PSMCs. Integrin $\alpha 1$ increases and $\alpha 5$ decreases the concentration of Ca²⁺, promoting intimal fibrosis. The binding between integrin $\alpha\text{v}\beta 3$ and OPN activates FAK signal transduction, which might be involved in the processes of vascular remodelling. The right part of the circle shows the role of integrins in renal fibrosis in ADPKD. Integrin $\alpha\text{v}\beta 3$ expressed in renal tubular epithelial cells binds with periostin, activating TGF- β and promoting renal fibrosis. Binding between integrin $\alpha\text{v}\beta 3$ and OPN is also involved in the renal fibrosis process, but the underlying mechanism is unclear. Renal tubular epithelial cells expressing integrin $\beta 1$ enhance the expression of collagen, fibronectin, and α -SMA, which promote renal fibrosis.

Fig. 7. Main roles of integrins in the process of AS. Integrin signaling can affect multiple processes in AS, including endothelial dysfunction and activation, leukocyte homing to the plaque, smooth muscle cell migration, and thrombosis. In the process of endothelial cell activation, ox-LDL activates $\alpha 5\beta 1$, induces the FAK/ERK/p90RSK pathway and promotes NF- κ B signaling. Shear stress can activate $\alpha\text{v}\beta 3$ and induce PAK activation by binding to fibronectin, thereby promoting NF- κ B activation. Both ox-LDL and shear stress generated by blood flow mediate the increased expression of proinflammatory genes (ICAM-1 and VCAM-1) after integrin ligation. During the process of leukocyte homing to plaques, $\alpha\text{x}\beta 2$ and $\alpha 4\beta 1$ interact with VCAM-1 on the endothelial cell surface, and $\alpha\text{x}\beta 2$ and $\alpha\text{L}\beta 2$ interact with ICAM1 to promote leukocyte adhesion. Integrins $\alpha 4\beta 1$, $\alpha 9\beta 1$ and $\alpha\text{v}\beta 3$ on the surface of monocytes interact with osteopontin, which is expressed in atherosclerotic plaques, to promote monocyte migration and survival. Integrin $\alpha\text{D}\beta 2$ is upregulated during macrophage foam cell formation. During vascular smooth muscle cell migration, $\alpha\text{v}\beta 3$ binding with fibronectin, osteopontin, etc., mediates FAK activity and drives migration. In the process of thrombosis, integrins $\alpha 2\beta 1$ and $\alpha\text{IIb}\beta 3$ on platelets are involved in platelet adhesion, activation, aggregation and thrombosis.

Table 1. Integrins expression involved with SARS-CoV-2 infection.

Table 2. The targeting integrin-related indications in clinical trials.

Table 3. Recent integrin-targeting drugs intended as disease therapies in ongoing clinical studies (2019-2022).

Table 4. Integrin-targeting therapies in clinical trials.

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